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Batch Production of a Potent Small Molecule Active Pharmaceutical Ingredient

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Abstract

Small molecule Active Pharmaceutical Ingredients (APIs) have become increasingly relevant in cancer treatment due to their efficacy, targeted treatment, and clinical value. Commonly manufactured in a batch pharmaceutical process, APIs must satisfy Critical Quality Attributes (CQAs) including chemical purity and physical properties. This process involves a multitude of steps, components, and equipment that are optimized to produce an API in a timely and cost-efficient manner. Here, we consider the process and facility design of a batch production of Halfaxia, a new potent anti-cancer drug from Johnson & Johnson. The process begins with a reaction of a starting material and a second reagent in tetrahydrofuran (THF). Following reaction completion, THF is exchanged for ethanol in a technique known as solvent swap distillation. Next, the API undergoes dry seed crystallization in ethanol. The crystals are then filtered out using Nutsche filtration and vacuum drying, producing Halfaxia in powder form. The process involves a 4000-Liter jacketed vessel and a Nutsche filter dryer, as well as heat exchangers, pumps, and pressure vessels for storage. The process will produce 184 kg of API in 77 hours with a 99.8% conversion, which satisfies the objective of producing 100 kg of product. The facility is designed to limit operator interaction and exposure to the API and other chemical compounds that are hazardous to human health. This process design has an NPV of $488 million, an ROI of 400%, and an IRR of 332%, which proves to be very profitable. However, due to confidentiality reasons, the costs of research and development, clinical trials, and FDA approval have been ignored. J&J should pursue further laboratory-scale experimentation and re-run the models using confidential data and figures before the company makes a final decision on the implementation of this process.

Disciplines

Biochemical and Biomolecular Engineering | Chemical Engineering | Engineering

April 21, 2020
Department of Chemical and Biomolecular Engineering
School of Engineering and Applied Sciences
University of Pennsylvania
220 S. 33rd Street
Philadelphia, PA 19104

Dear Mr. Bruce Vrana, Dr. Miriam Wattenbarger, and Dr. Alex Marchut,

Enclosed is a process design and production facility for a batch production of a potent small molecule active pharmaceutical ingredient (API), as proposed by Dr. Alex Marchut of Johnson & Johnson (J&J). The API, hypothetically named Halfaxia, is an anti-cancer drug that can be produced via a first-order reaction, distillation, crystallization, filtration, and drying steps. This process will produce 184 kg of API powder in 77 hours, which is on the order of typical API production processes.

The production facility has been designed with the possibility of handling different complex and simple future API processes, and with consideration for the operators' safety from health hazards associated with API production. The reaction, distillation, and crystallization of the process will be conducted in a single reaction vessel, while filtration and drying will occur with separate filter dryer equipment. The facility will be built as an extension to a pre-existing J&J production site in Mumbai, India. Rigorous profitability analysis has been conducted on this design and facility to ensure minimal operation and equipment costs. The analysis shows a net present value (NPV) of $488 million and a return on investment (ROI) of 400%. The internal rate of return (IRR) is 332%, which satisfies the client requirement of at least 20% IRR. Costs for research and development, clinical trials, FDA approval, and drug product delivery have been omitted due to confidentially and must be implemented to gain a full understanding of profitability.

Since the process and facility design is shown to be profitable, we recommend moving forward with the proposal, but we note that additional testing of equipment and optimal parameters may be required to ensure the validity of our design. Guidance throughout the semester was provided by Dr. Wattenbarger, Dr. Marchut, and various engineering consultants.

Sincerely,

Isuru Amarasekera | Jinwan Cho | Jason Li

Batch Production of a Potent Small Molecule Active Pharmaceutical Ingredient

Isuru Amarasekera

Jinwan Cho

Jason Li

Proposed by Dr. Alex Marchut

Project Advisor: Dr. Miriam Wattenbarger

University of Pennsylvania

School of Engineering and Applied Sciences

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April 21, 2020

Table of Contents

Section 1: Abstract

1. Abstract

Small molecule Active Pharmaceutical Ingredients (APIs) have become increasingly relevant in cancer treatment due to their efficacy, targeted treatment, and clinical value. Commonly manufactured in a batch pharmaceutical process, APIs must satisfy Critical Quality Attributes (CQAs) including chemical purity and physical properties. This process involves a multitude of steps, components, and equipment that are optimized to produce an API in a timely and cost-efficient manner. Here, we consider the process and facility design of a batch production of Halfaxia, a new potent anti-cancer drug from Johnson & Johnson. The process begins with a reaction of a starting material and a second reagent in tetrahydrofuran (THF). Following reaction completion, THF is exchanged for ethanol in a technique known as solvent swap distillation. Next, the API undergoes dry seed crystallization in ethanol. The crystals are then filtered out using Nutsche filtration and vacuum drying, producing Halfaxia in powder form. The process involves a 4000-Liter jacketed vessel and a Nutsche filter dryer, as well as heat exchangers, pumps, and pressure vessels for storage. The process will produce 184 kg of API in 77 hours with a 99.8% conversion, which satisfies the objective of producing 100 kg of product. The facility is designed to limit operator interaction and exposure to the API and other chemical compounds that are hazardous to human health. This process design has an NPV of $488 million, an ROI of 400%, and an IRR of 332%, which proves to be very profitable. However, due to confidentiality reasons, the costs of research and development, clinical trials, and FDA approval have been ignored. J&J should pursue further laboratory-scale experimentation and re-run the models using confidential data and figures before the company makes a final decision on the implementation of this process.

Section 2: Introduction and Objective-Time Chart

2.1 Background

Approximately 38% of men and women in America will be diagnosed with cancer at some point throughout their lifetime [1]. This high volume of cancer patients indicates a need for a consistent and reliable method to manufacture cancer treating active pharmaceutical ingredients (APIs). An API is defined as any substance or mixture of a substance that becomes an active ingredient of a drug product. One of the most common methods to produce APIs in the pharmaceutical industry includes batch processing, which is the step-by-step creation of various components of a drug [2]. Most small molecule APIs are chemically synthesized in larger batches, on the order of 100 kg. Batch processes to create an API range from a simple homogeneous liquid reaction and crystallization to complex intermediate steps such as extraction and distillation. In either situation, filtration and drying are used and, depending on the crystallization process and particle size requirements, a final milling step may be added. Batch processes have been used in the pharmaceutical industry for decades and the industry rarely deviates from these systems to produce drugs.

2.2 Motivations and Goals

Janssen Pharmaceuticals, the biopharmaceutical division of J&J, has proposed a project to design a 100 kg batch manufacturing process for a potent small molecule active pharmaceutical ingredient. The API's chemical makeup and function remains confidential and follows the pseudonym Halfaxia. Actual kinetic data for the chemical reaction, crystallization information, and time considerations for the batch processes were provided by J&J. In addition, the solvent for the API reaction and crystallization has been set as tetrahydrofuran (THF) and denatured ethanol, respectively. The processing steps and conditions were designed and optimized independently. The process includes a series of steps that occur in the same jacketed batch reactor: reaction in

THF, distillation solvent swap, and crystallization in ethanol. Additional steps include filtering, washing, and drying the API product before safe collection. Another proposed component of this project includes designing the manufacturing facility, which is assumed to be part of a co-existing pharmaceutical plant. For efficiency and economic purposes, this small molecule API manufacturing facility must be flexible enough to handle a range of simple to complex processes. Therefore, this facility was designed to produce Halfaxia in addition to other similar low exothermic APIs. Additionally, many APIs present hazards to human health with exposure to large quantities of the product. The facility was produced with careful consideration of hazards and toxins by minimizing exposure between the operator and API.

J&J provided an approximate raw material starting cost and approximate selling price of the API in its dried but unformulated state. This information, in addition to capital and operating costs for the manufacturing process, was used to optimize the NPV of the process to earn at least a 20% IRR on the investment. The IRR goal provided guidelines for how long the batch process must take and how many batches must be completed per year. Although the minimum requirement for each batch is 100 kg of API product, this value was maximized for economic purposes in the design of the process.

2.3 Objective-Time Chart

Project Name	Batch Production of a Potent Small Molecule Active Pharmaceutical Ingredient
Project Author	Dr. Alex Marchut, Johnson & Johnson, Janssen Biopharmaceuticals Division
Project Advisor	Dr. Miriam Wattenbarger, Department of Chemical and Biomolecular Engineering
Project Leaders	Isuru Amarasekera, Jinwan Cho, and Jason Li
Specific Goals	- Design a manufacturing process to synthesize Halfaxia, a confidential anti-cancer API using provided data - Design a flexible and safe production facility capable of handling various batch processes while minimizing exposure between the API and operator
Project Scope	*In Scope* - Optimize reaction conversion, distillation separation, and crystallization yield - Design a robust process including equipment design and process conditions while focusing on detailed Halfaxia synthesis - Determine heat utilities required throughout low exothermic process - Design a facility for housing this process - Incorporate safety conditions for handling hazardous solvents and volatile organic pollutants such as THF and the API - Minimize capital costs of the equipment and operating costs of the facility to achieve at least an 20% IRR on the process
	Out of Scope - Design process for high exothermic reactions - Incorporate costs of research and development, clinical trials, FDA regulations, and direct transportation costs of raw materials and products - Design of rigorous process control system - Verification of assumptions and supplied information from the project statement - API quality check for purity of product
Deliverables	- Mass and energy balances

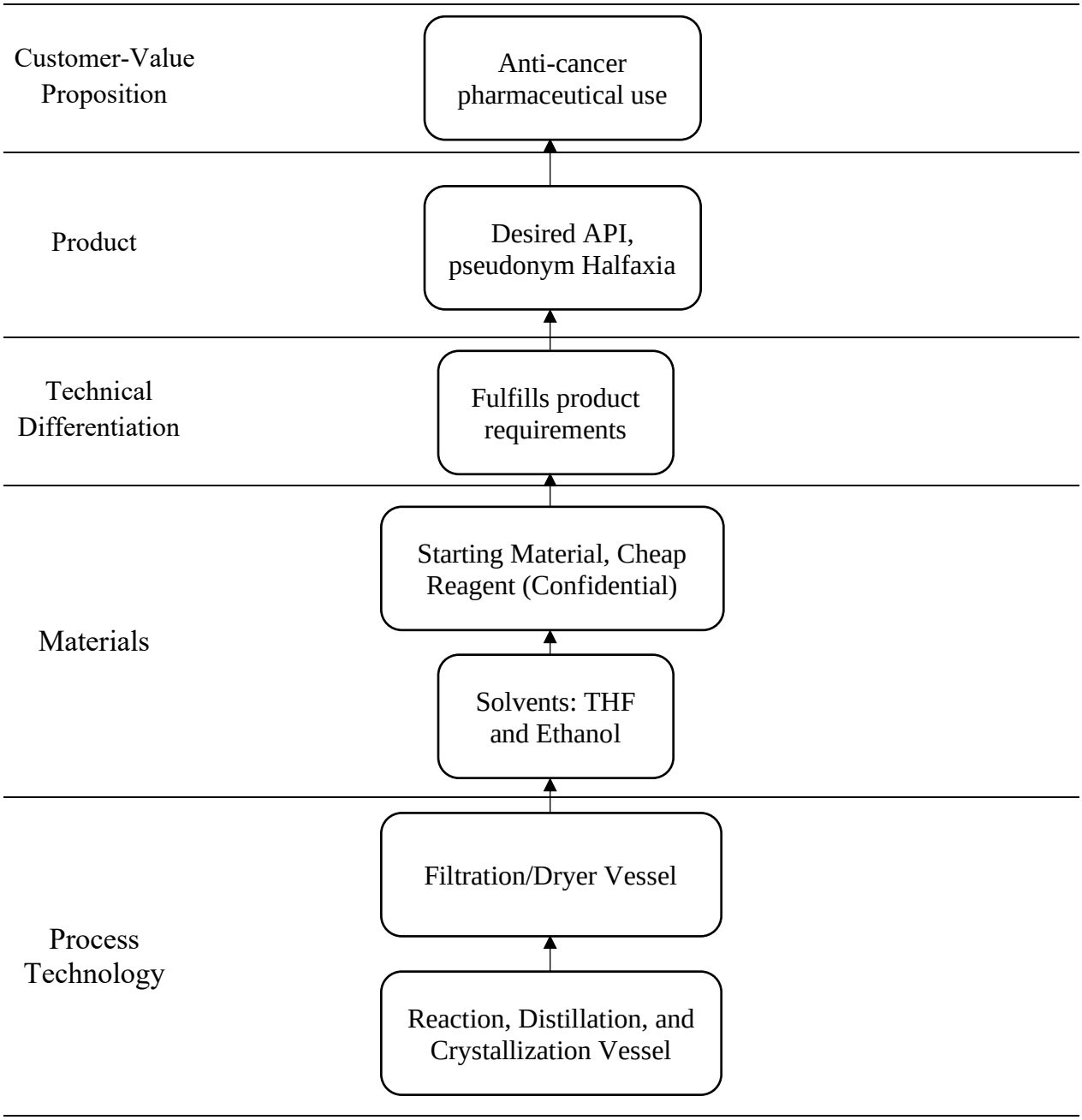
	- Process flow diagram and Aspen simulation results - Equipment design and cost - Economic and profitability analysis on process - Written report and presentation
Timeline	The objectives and deliverables will be completed from January to April 2020. Deadlines: - Initial Project Presentation: November 25th, 2019 - Preliminary Mass Balance Completed: February 4th, 2020 - Mid-Semester Presentation: March 3rd, 2020 - Final Energy Balance Completed: March 17th, 2020 - Major Equipment Designed: March 24th, 2020 - Finances Completed: April 7th, 2020 - Report Draft Competed: April 14th, 2020 - Final Report Submitted: April 21st, 2020 - Final Presentation: April 28th, 2020

2.4 Calendar

	Week 1	Week 2	Week 3	Week 4
January			Complete preliminary research	
February	Complete mass balance spreadsheet		Complete Aspen batch distillation simulation Complete process flow diagram	
March		Complete energy balance spreadsheet Give mid-semester presentation		Finish major equipment design
April	Complete finances and profitability analysis		Submit final draft of report	Give final presentation

Section 3: Innovation Map

3.1 Innovation Map



Section 4: Market and Competitive Analyses

4.1 Market Sizing and Applications

The cancer API market has been exponentially developing around the world due to clinical value and efficacy of the products. The global API market size is valued at 170.8 billion USD in 2019 and is expected to grow at progressive 6.7% CAGR while earning a high level of revenue in the forecast period [3]. Major factors that have influenced the growth of the market include increased trends of offshore manufacturing and need for cancer treating products with reduced adverse side effects. Small molecules account for 80% of pharmaceutical sales, which indicates their relevance in the future of the pharmaceutical industry. While many pharmaceutical companies are located in the United States, most API manufacturers are located in Asia [4].

4.2 Competitive Analysis

The cancer API market is currently led by North America with the major players including Exelixis Inc, Pfizer Inc, Eisai Ltd, Bristol-Myers Squibb, and AstraZeneca plc. J&J's biopharmaceutical division is currently not a top competitor in the API space, which indicates a desire to join the market. Although these competitors dominate in extensive research and development efforts, actual API production requires immense capital costs due to systematic protocols. Therefore, several pharmaceutical companies benefit from outsourcing API production to eliminate costs of labor and installation fees for the manufacturing units. The leading manufacturer of APIs is Teva Active Pharmaceutical Ingredients (TAPI), which produces the industry's largest portfolio of over 300 API products [5]. The API market is mainly divided between the captive market (internal production by pharmaceutical companies) and the merchant market (API production through third party providers) [6]. Figure 4.2.1 shows how external production of APIs has a consistently higher market size than internal production. Additionally, the merchant market has been steadily dominating over the years, supporting the notion that third-

party manufacturing facilities maximize economic potentials.

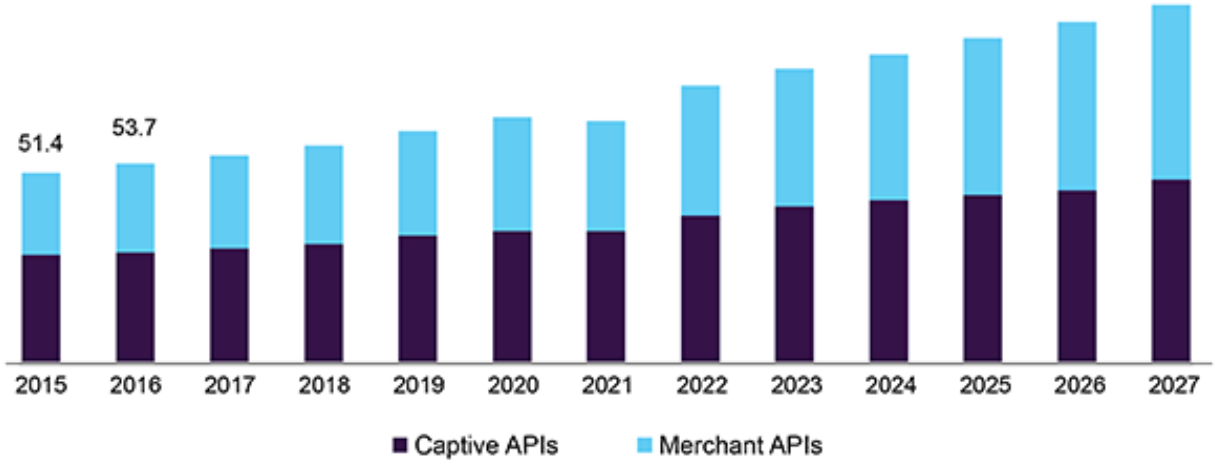


Figure 4.2.1 U.S API Market Size by type of Manufacturer in USD Billion from 2015-2027

While outsourcing API production has helped pharmaceutical companies cut costs on expensive equipment, concern arises towards the quality of the APIs produced overseas. Regulations have helped mitigate these risks to validate the purity and efficacy of the API products. Although the market indicates preference towards outsourcing API production, large pharmaceutical companies may benefit from developing a manufacturing process that is flexible enough to handle a wide array of pharmaceutical production [7].

4.3 Confidentially Statement

The API produced in this project must remain confidential, which includes its function, mechanism of action, and certain physical properties. The expected selling price, demand, and customer segmentation are also unknown. Additionally, the process must be designed without knowing if the drug will only be sold in the United States or if it reaches an international market. For these reasons, there is flexibility in where the manufacturing process may be located. Although the function of the drug remains confidential, the overall need for APIs in cancer treating therapeutics remains relevant for the motivation in creating a robust manufacturing process.

Section 5: Customer Requirements

5.1 Customer Requirements

Typical critical quality attributes of the API produced in this process include chemical purity, solid form, and particle size. However, due to the confidentiality of the product, the exact customer requirements are unknown. Additionally, the API produced in this batch process will not be in the final form for customers. Halfaxia must be sent to a co-located drug product site to create the final sellable form, which includes milling, mixing the API with pharmaceutical excipients, and producing delivery methods.

Although the customer requirements for the API product are unknown, the actual batch pharmaceutical process and facility have key specifications. The API manufacturing process must produce at least 100 kg of API product per batch with a minimum 20% IRR on investment. The plant may be located anywhere around the world where supplies of utilities are readily available. Although the drug product site requires a nearly 99% pure API product, the final purification is beyond the scope of the project. Additionally, the manufacturing process must be flexible enough to handle various batch processes with proper cleaning and maintenance in between batches. The facility must be designed to minimize exposure between the API and the operators. Lastly, the API has known solvents for the process, which include THF for the reaction and ethanol for the crystallization. The complete list of chemical properties and requirements is described in Section 11.

Section 6: Critical-to-Quality Variables - N/A

Section 7: Product Concepts - N/A

Section 8: Superior Product Concepts - N/A

Section 9: Competitive Patent Analysis - N/A

Section 10: Preliminary Process Synthesis

10.1 Preliminary Process Synthesis

Due to the confidential nature of the drug's chemical and physical properties, alternatives for the main production processes of reaction, distillation, and crystallization could not be considered. However, alternative operational choices were considered for these production processes.

10.2 Vacuum Distillation

For the distillation step, distillation in a vacuum was considered. At 1.1 bar, ethanol and THF form a low boiling azeotrope, but the azeotrope is no longer present when the pressure is reduced to a near vacuum. However, the dew point temperatures for the mixture is very low in a near vacuum, meaning the solubility of the API in the solution is also extremely low. As such, vacuum distillation was not chosen because much more solvent would be required to keep the API dissolved throughout the distillation, significantly increasing capital costs. Furthermore, the low API solubility would limit the amount of API that could be recovered through crystallization, which relies on the reduction in solubility as the temperature of the solution is reduced. Therefore, the process was designed to maximize the amount of API recovered.

10.3 Recycling of Ethanol and THF in the Distillate

The distillation process described in this report involves a large amount of ethanol and THF in the distillate that are disposed of instead of being recycled. Although the recycling process would require a separation of the ethanol and THF and thus additional equipment, the reduction in material costs would have likely decreased the operating costs significantly over time such that any increase in capital cost would have been offset. However, J&J did not recommend recycling any solvents simply because the processes produces an important drug, and using recycled solvents are not desired even if the likelihood contamination is low. Overall, the cost of the THF and ethanol

are minimal compared to the cost of the starting material and the product, so the small economic benefit did not justify recycling solvents that risks potential contamination.

Another avenue that was explored involved selling the distillate as a by-product to a third-party company that would use more rigorous distillation efforts to separate the THF and ethanol. However, the economic gains from selling the distillate would most likely be minimal compared to the overall profitability of the API. Additionally, the Halfaxia manufacturing facility would have to verify if any API is present in the distillate before selling it to third party companies. Otherwise, companies are unlikely to purchase potentially contaminated distillate that would require extensive containment protocols. Therefore, the distillate is not sold in this process.

Section 11: Assembly of Database

11.1 Properties of Materials

The manufacturing process primarily uses two solvents: tetrahydrofuran (THF) and ethanol. The physical properties of the two solvents were compiled from PubChem and are shown in Table 11.1.1. These properties were measured at room temperature (20 °C) and atmospheric pressure (1 bar). Properties such as density that changed with temperature were separately acquired using ASPEN simulations, as described in Section 11.1.2.

Table 11.1.1 Properties of Solvents

Solvent	Molecular Formula	Molecular Weight (g/mol)	Boiling Point (°C)	Melting Point (°C)	Density (g/mL)
THF	C_4H_8O	72.11	65.0	-108.3	0.888
Ethanol	C_2H_6O	46.07	78.2	-114.1	0.789

The identity and most properties of the starting material, a second reagent, and the product were unavailable due to confidentiality. The molecular weight of the starting material was assumed to be 500 daltons since this value is the typical lower bound for the molecular weight of a pharmaceutical small molecule [8]. The product was also assumed to have reaction properties and a similar molecular weight as aspirin (molecular weight of 180 daltons), a comparable representative small molecule drug as recommended by J&J. The density of the product, 0.23 grams/cm^3, was also provided by J&J. The properties of the second reagent were not required for the calculations in this process design.

Some data regarding the reaction kinetics of the starting material in THF were available, tabulated in Table 11.1.2. The reaction follows Equation 11.1.1, with starting material and second reagent reacting to create the API product. An excess of B was assumed in order to treat the reaction as first order. Additionally, the reaction kinetics were assumed to follow the Arrhenius equation shown in Equation 11.1.2. The heat of reaction of forming Halfaxia was assumed to be -27.1 kJ/mol, which corresponds to the heat of reaction of forming aspirin.

$$A+B \rightarrow C \quad \text{(Equation 11.1.1)}$$

A: Starting Material
B: Second Reagent
C: API Product, Halfaxia

$$k\left[\frac{L}{mol\cdot s}\right] = 2.91\times 10^{-4}\, e^{\frac{-8.95}{R\cdot T[k]}} \quad \text{(Equation 11.1.2)}$$

Table 11.1.2 Reaction Properties of Starting Material in THF

Pre-exponential factor, k_0 (L/mol·s)	2.91×10^{-4}
Activation Energy, E_a (J/mol)	8.95
Heat of Reaction, ΔH_{rxn} (kJ/mol)	-27.1

The liquid and vapor molar fraction of THF and ethanol as a function of temperature (T-XY diagram) was modeled using Aspen Plus's UNIQUAC method. The interaction between THF and ethanol occurs in the distillation solvent swap step. The graph is show in Figure 11.1.1.

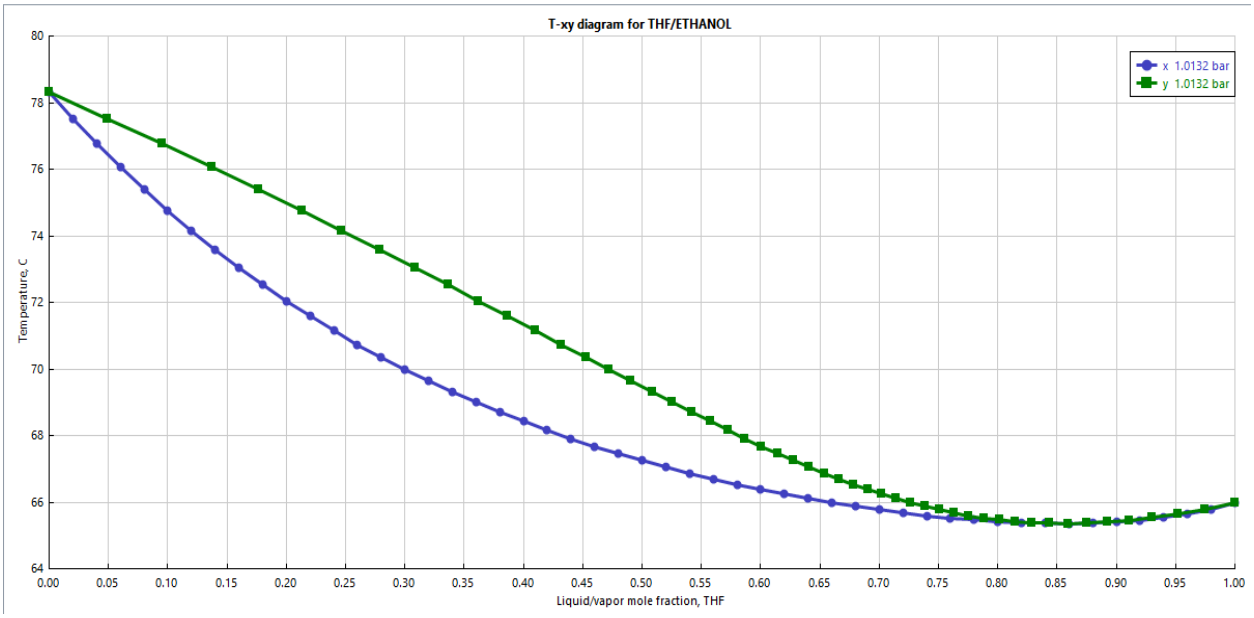


Figure 11.1.1 T-xy diagram for THF/Ethanol system.

The crystallization data of Halfaxia in ethanol as the solvent was provided by Dr. Marchut. The solubility of Halfaxia was given in mg/mL as a function of temperature. This data was necessary to determine the temperature conditions for crystallization and is shown in Figure 11.1.2.

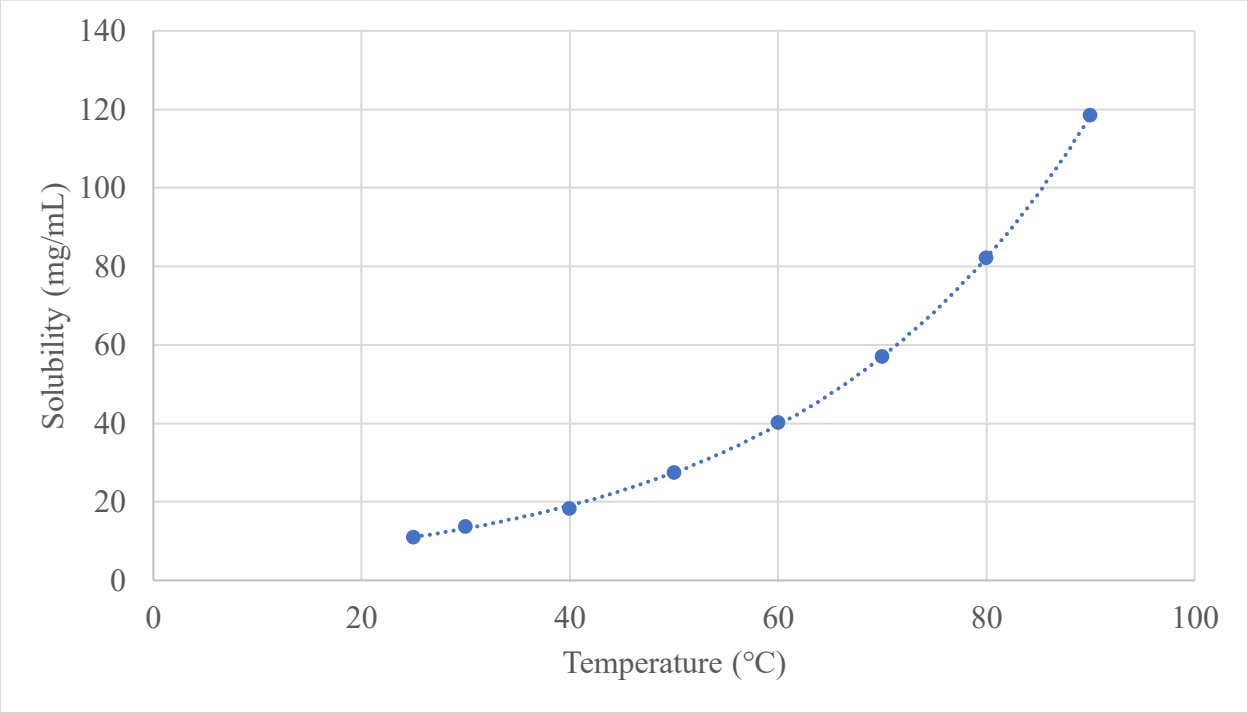


Figure 11.1.2 Solubility of Halfaxia as a function of temperature.

The exponential regression line associated with these data points, with an R^2 value of 0.9968, is:

$$\text{Solubility } [\frac{\text{mg}}{\text{mL}}] = 4.44e^{0.0365*\text{Temperature(°C)}}$$

Heat exchange is performed with 30% w/w ethylene glycol, water, and steam, so the density, heat capacity, thermal conductivity, and viscosity at varying temperatures were used. The properties of cooling water and steam were acquired from property tables on water and steam. The relevant properties of 30% w/w ethylene glycol were found by ASPEN simulation using the UNIQUAC method.

11.2 Aspen Plus Modeling Properties

Aspen Plus was used to model the batch distillation solvent swap step. The BATCHSEP block was used to model the batch distillation. The properties of THF, ethanol, and 30% w/w ethylene glycol were modelled on Aspen Plus using the UNIQUAC method. The reaction and crystallization steps could not be modeled using Aspen Plus, since the identity and composition of the starting material and the second reagent were not provided. Solubility and crystallization data were utilized with appropriate assumptions as described in Section 14.

11.3 Cost of Raw Materials

The approximate cost of ethanol and THF in bulk was requested from MilliporeSigma consultants. The cost of 30% w/w ethylene glycol was drawn from Sigma Aldrich's website. These costs are listed in Table 11.3.1, and they represent bulk orders in the year 2020. Using information provided by Johnson & Johnson, the cost of the second reagent is negligible. The cost for the starting material is confidential but the net profit of the API is $20 per gram. The confidentiality exists because the cost of the API does not reflect the price of the drug, and the price and cost will change depending on costs incurred during the R&D stage. The starting material is assumed to cost 10$/gram while the selling price of the API is 30$/gram. All materials are pharmaceutical-grade and used for industrial purposes.

Table 11.3.1 Cost of Raw Materials

Material	Cost ($/g)
Ethanol	0.005
THF	0.12
30% w/w Ethylene Glycol	0.0014
Starting Material	10

Section 12: Process Flow Diagram and Material Balances

12.1 Process Flow Diagram

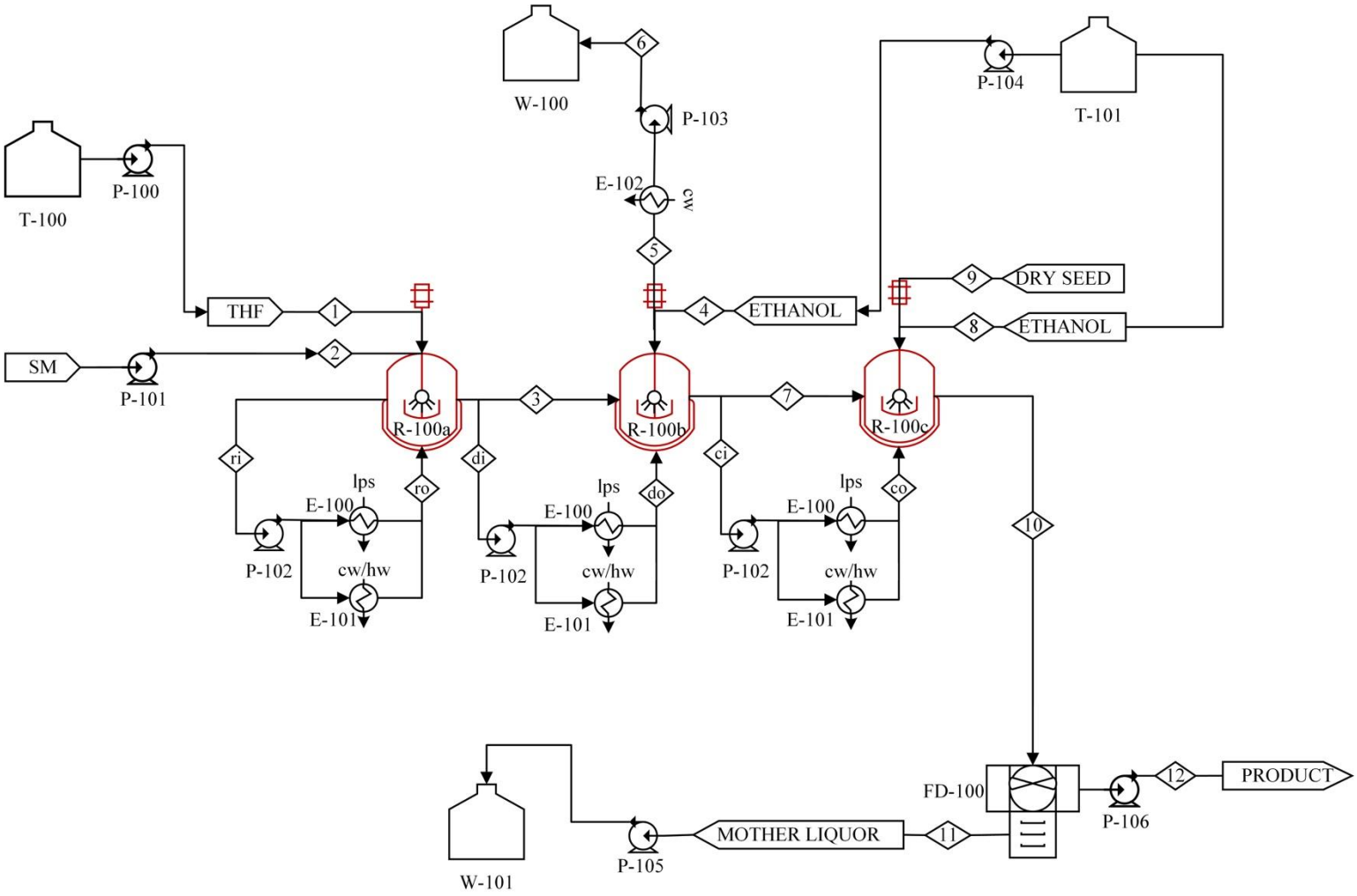


Figure 12.1.1 Process Flow Diagram for Halfaxia API Batch Processing. The reaction, distillation, and crystallization steps occur in the same vessel denoted by the red outline and labels R-100(a-c).

Some key elements of the PFD must be identified. Ri, di, and ci represent the stream leaving the jacket and entering the heat exchanger. Ro, do, and co represent the stream leaving the heat exchanger and entering the jacket. The utilities are designed in the process as low pressure steam (lps), hot water (hw), cooling water (cw, present for E-102), and chilled water (cw, present for E-101).

12.2 Material Balances for API Manufacturing Process

Table 12.2.1 describes the overall mass balance for Halfaxia synthesis without the external heat exchanger system and jacket fluid conditions. Due to the batch operation, the conditions of the streams, including mass composition and temperature, vary with time. However, Table 12.2.1 ignores transient conditions and displays the final values after each step has been completed, following the timeline in Table 12.3.1. Additional information on the mass flow rate of stream 4, the ethanol addition for the solvent swap, is described in Section 13.3.

Table 12.2.1 Stream Compositions and Conditions for Main Components of Process

Stream Number	**1**	**2**	**3**	**4**	**5**	**6**
Temperature (°C)	20	20	50	20	80	20
Pressure (bar)	1	1	1	1	1	1
Mass (kg)	2042.29	200.33	2242.62	6913.01	7126.41	7126.41
Component Mass: (kg)						
THF	2042.29	0	2042.29	0	2030.19	2030.19
Ethanol	0	0	0	6913.01	5096.22	5096.22
Starting Material	0	200.33	0.38	0	0	0
Product	0	0	199.95	0	0	0
Dry Seed	0	0	0	0	0	0
30% w/w Ethylene Glycol	0	0	0	0	0	0

Stream Number	**7**	**8**	**9**	**10**	**11**	**12**
Temperature (°C)	80	20	20	12	12	20
Pressure (bar)	1	1	1	1	1	1
Mass (kg)	2029.22	145.06	1	2175.28	1991.42	183.86
Component Mass: (kg)						
THF	12.10	0	0	12.10	12.10	0
Ethanol	1816.79	145.06	0	1961.85	1961.85	0
Starting Material	0.38	0	0	0.38	0.38	0
Product	199.95	0	0	200.95	17.09	183.86
Dry Seed	0	0	1.00	0	0	0
30% w/w Ethylene Glycol	0	0	0	0	0	0

The jacket fluid conditions at each step in the process are displayed in Tables 12.2.2, 12.2.3, and 12.2.4. Each table shows the changes in jacket fluid in the order in which they occur. The jacket only contains 30% w/w ethylene glycol that flows continuously through the tube side of the desired heat exchanger, E-100 (steam) or E-101 (chilled water). For each step, the tables indicate the active equipment, time of operation, and utility used.

The operational steps can be divided into two categories based on the goal. First, the process steps involve changing the vessel temperature to carry out a manufacturing process, such as distillation; for these steps, the jacket temperature is desired to be maintained in order to accurately control the vessel temperature. Second, the intermediate steps involve changing the jacket fluid temperature in between process steps; the goal of these steps is to change the jacket fluid temperature to the desired temperature required for the next process step. Although the times for the intermediate steps are tabulated in Table 12.2.2, they actually occur at the end of each the process step; because there is a time delay for the temperature of the jacket fluid to be changed in the heat exchanger and circulated into the jacket, the intermediate steps occur just before each process step is schedule to end, allowing the jacket fluid that had just been heated or cooled to enter the jacket just as the next process step begins. As such, the durations of the intermediate steps were not included in the overall timeline of the process (shown in Table 12.3.1), but they were used to accurately account for utility costs.

Table 12.2.2 Outline of Jacket Fluid Conditions for the Reaction as a Function of Time

Stream Number	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**
Goal	*Heat Jacket Fluid from 20 to 60 °C*		Heat *R-100a contents* from 20 to *50 °C*		*Cool Jacket Fluid from 60 to 50 °C*		*Maintain R-100a contents at 50 °C*	
Jacket Fluid Temperature (°C)	20	60	55	60	60	50	49	50
Pressure (bar)	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	2.20	2.20	2.20	2.20	0.91	0.91	0.91	0.91
Operation Time Per Batch (hr):	0.076		0.77		0.18		6.00	
Equipment Active:	R-100a, E-100, P-102		R-100a, E-101, P-102		R-100a, E-101, P-102		R-100a, E-101, P-102	
Utility:	lps		hw		hw		hw	

Table 12.2.3 Outline of Jacket Fluid Conditions for Distillation as a Function of Time

Stream Number	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**
Goal	*Heat Jacket Fluid from 50 to 85 °C*		*Heat R-100b contents from 50 to 68 °C*		*Heat Jacket Fluid from 90 to 102 °C*		*Carry out Solvent Swap in R-100b*	
Jacket Fluid Temperature (°C)	50	85	85	90	90	102	97	102
Pressure (bar)	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	3.45	3.45	3.45	3.45C	3.72	3.72	3.72	3.72
Operation Time Per Batch (hr):	0.05		0.51		0.04		18.80	
Equipment Active:	R-100a, E-100, P-102		R-100a, E-100, P-102		R-100a, E-100, P-102		R-100a, E-100, P-102	
Utility:	lps		lps		lps		lps	

Table 12.2.4 Outline of Jacket Fluid Conditions for Crystallization as a Function of Time

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Goal	*Cool Jacket Fluid from 102 to 70 °C*		*Cool R-100c contents from 80.2 to 77.2 °C*		*Heat Jacket Fluid from 70 to 77 °C*		*Hold R-100c Contents at 77 °C*		*Cool Jacket Fluid from 77 to 69 °C*		*Cool R-100c contents from 77.2 to 72 °C*		*Cool Jacket Fluid from 69 to 64 °C*		*Cool R-100c contents from 72 to 67 °C*	
Jacket Fluid Temperature (°C)	102	70	75	70	70	77	77	78	77	69	71	69	69	64	66	64
Pressure (bar)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	1.00	1.00	3.90	3.90	1.06	1.06	1.06	1.06	1.05	1.05	1.05	1.05	1.01	1.01	1.01	1.01
Operation Time Per Batch (hr):	0.17		0.30		0.16		3.00		0.16		1.00		0.16		1.00	
Equipment Active:	R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102	
Utility:	hw		hw		hw		hw		hw		hw		hw		hw	

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Goal	*Cool Jacket Fluid from 64 to 59 °C*		*Cool R-100c contents from 867 to 62 °C*		*Cool Jacket Fluid from 59 to 54 °C*		*Cool R-100c contents from 62 to 57 °C*		*Cool Jacket Fluid from 54 to 49 °C*		*Cool R-100c contents from 57 to 52 °C*		*Cool Jacket Fluid from 49 to 43 °C*		*Cool R-100c contents from 52 to 47 °C*	
Jacket Fluid Temperature (°C)	64	59	61	59	59	54	56	54	54	49	51	49	49	43	46	43
Pressure (bar)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	1.04	1.04	1.04	1.04	1.05	1.05	1.05	1.05	1.07	1.07	1.07	1.07	1.15	1.15	1.15	1.15
Operation Time Per Batch (hr):	0.16		1.00		0.16		1.00		0.16		1.00		0.14		1.00	
Equipment Active:	R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102	
Utility:	hw		hw		hw		hw		hw		hw		hw		hw	

Table 12.2.4 (cont.) Outline of Jacket Fluid Conditions for Crystallization as a Function of Time

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Goal	*Cool Jacket Fluid from 43 to 38 °C*		*Cool R-100c contents from 47 to 42 °C*		*Cool Jacket Fluid from 38 to 32 °C*		*Cool R-100c contents from 42 to 37 °C*		*Cool Jacket Fluid from 32 to 27 °C*		*Cool R-100c contents from 37 to 32 °C*		*Cool Jacket Fluid from 27 to 21 °C*		*Cool R-100c contents from 32 to 27 °C*	
Jacket Fluid Temperature (°C)	43	38	41	38	38	32	35	32	32	27	30	27	27	21	24	21
Pressure (bar)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	0.93	0.93	0.93	0.93	1.08	1.08	1.08	1.08	1.04	1.04	1.04	1.04	1.05	1.05	1.05	1.05
Operation Time Per Batch (hr):	0.18		1.00		0.15		1.00		0.16		1.00		0.16		1.00	
Equipment Active:	R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102	
Utility:	hw		hw		cw		cw		cw		Cw		cw		cw	

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Goal	*Cool Jacket Fluid from 21 to 15 °C*		*Cool R-100c contents from 27 to 22 °C*		*Cool Jacket Fluid from 15 to 9 °C*		*Cool R-100c contents from 22 to 17 °C*		*Cool Jacket Fluid from 9 to 7 °C*		*Cool R-100c contents from 17 to 12 °C*	
Jacket Fluid Temperature (°C)	21	15	18	15	15	9	12	9	9	7	11	7
Pressure (bar)	1	1	1	1	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.02	1.02	1.02	1.02
Operation Time Per Batch (hr):	0.15		1.00		0.15		1.00		0.16		2.00	
Equipment Active:	R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102		R-100c, E-101, P-102	
Utility:	cw		cw		cw		cw		cw		cw	

Table 12.3.1 Duration of key steps in process

Process	Time (hrs)
Heat reaction contents from 20 to 50 °C	0.77
Carry out reaction	6
Heating distillation contents from 50 to 68 °C	0.51
Carry out solvent swap distillation	18.8
Cool crystallization contents from 80.2 to 77.2 °C	0.30
Hold at supersaturation temperature, 77.2 °C	3
Final cooling to 12 °C	17.30
Filtration	6
Drying	24
Cleaning (occurs simultaneously with drying)	12
Total Time	**76.8**

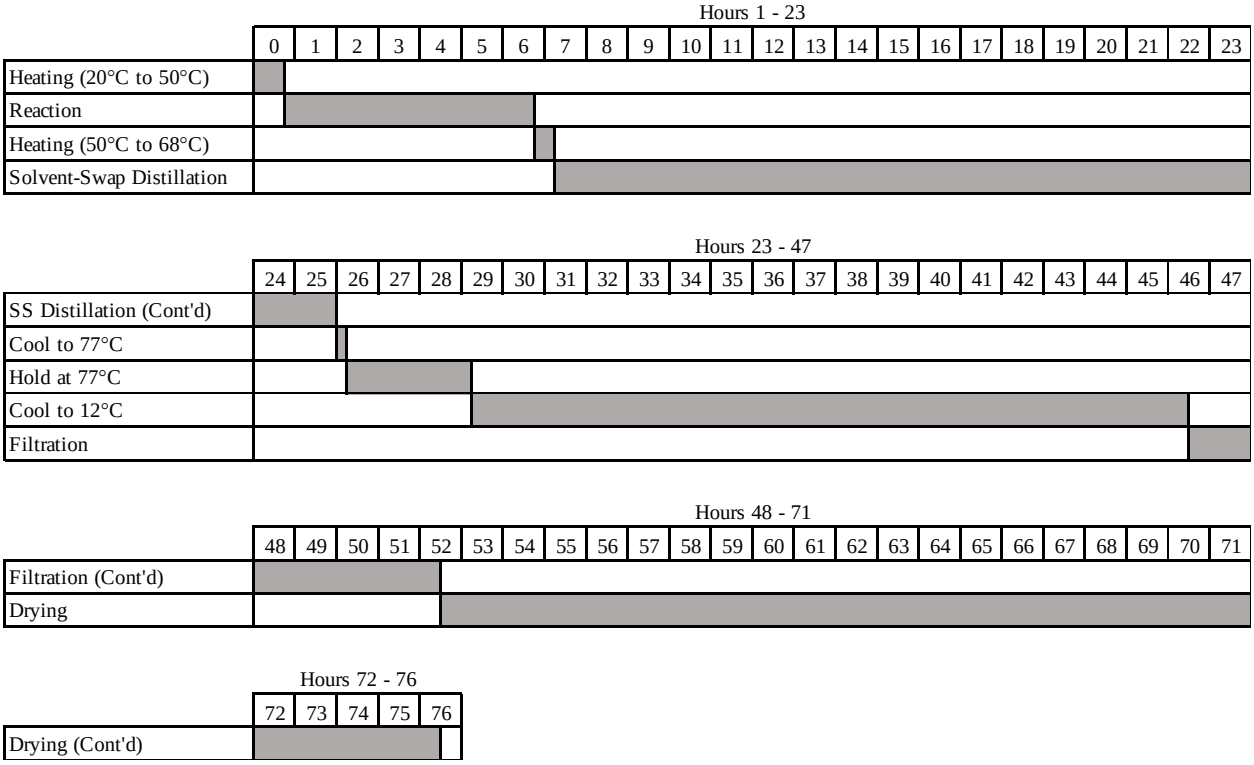


Figure 12.3.1 Timeline representation of the process. One batch takes approximately 77 hours, excluding cleaning.

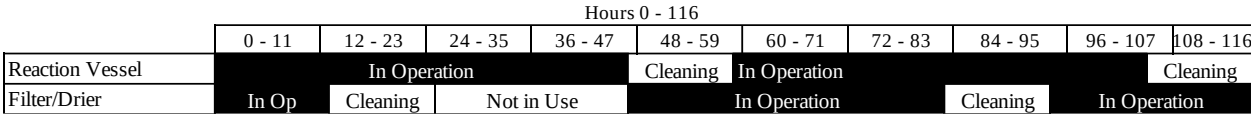


Figure 12.3.2 Timeline schematic representing the cleaning and operation cycles of the reaction vessel and the filter/dryer. Two batches will take approximately 117 hours total, including cleaning time, and assuming equipment is running 24 hours.

Section 13: Process Synthesis

13.1 Summary of Process

Shown in Figure 12.1.1 is the process flow diagram for the batch production of Halfaxia, a confidential API. The process contains three main steps: reaction, distillation, and crystallization. Following these steps, the product is then transferred to a filter dryer, in which the product assumes its final dry powder form. The first three processes occur in a single De Dietrich AE-4000 glass-lined reactor, shown as R-100 in Figure 12.1.1, which is equipped with a jacket containing 30% w/w ethylene glycol. Two external heat exchangers, shown as E-100 and E-101, are used to heat or cool the jacket fluid, which subsequently controls the temperature of the vessel contents by varying the jacket fluid temperature and flow rate. The vessel also comes with spray nozzles and agitators to assist in certain process requirements. The slurry created from crystallization is then sent to a filter dryer, shown as FD-100 in Figure 12.1.1, which separates the mother liquor from the final API product using the Nutsche filtration technique. A final ethanol washing step is implemented by depositing ethanol through spray balls built into the main vessel to wash the sides of the vessel and recover any product. The ethanol washes through the main vessel and into the filter dryer containing the product, giving the wet cake another wash. The ethanol washing step also helps to remove impurities from the final cake of product. This API batch manufacturing process creates 184 kg of product in 77 hours, which includes the time for filtering and drying. Information regarding detailed calculations for each step in the mass balance can be found in section 25.2 of the Appendix.

13.2 Reaction

The reaction, the details of which are largely unavailable due to confidentiality, was shown to be 1st order in A, the main starting material, in the presence of excess B, the cheaper starting material. The starting material and the cheaper starting material will arrive at the facility in

55-gallon stainless steel drums. Due to confidentiality, information about the cheaper starting material B was unavailable and therefore omitted from the PFD. The reaction is known to take place in THF with only the pre-exponential factor and the activation energy available, the details of which are described in Section 11. To minimize losses of starting material A, the initial concentration of A, the time of operation, and the operating temperature are all optimized. Since the API has a maximum solubility of 87 mg/ml in THF, the final concentration of the API needs to be set below 87 mg/ml to prevent precipitation. Precipitation of the API at this stage in the process is not desirable because product crystallization cannot be controlled precisely. Additionally, precipitation would result in a higher rate of fouling in the vessel and result in longer cleaning times. For these reasons, the final concentration of the API was controlled such that the API remained soluble until crystallization. Furthermore, the reaction conversion needed to be maximized in order to minimize losses of the costly starting material. To this end, the initial concentration of A was set to 87.1 mg/ml, and the reaction was carried out at 50 °C over 6 hours. The temperature was set below the boiling point of THF to prevent loss of reaction solvent as well as significant vapor pressure during the reaction. Thus, the temperature was selected to optimize between high reaction rate and high heat duty. The initial concentration of 87.1 mg/ml was the highest allowable concentration of starting material that resulted in a final API concentration of 87 mg/ml while simultaneously maximizing the reaction rate. The resulting conversion was calculated to be 0.998 over 6 hours at 50 °C, which is verified through simulations in Section 25.5 of the Appendix.

As shown in Figure 12.1, the reaction takes place in R-100a, a glass-lined stainless steel vessel that was recommended based on industry standard for J&J for avoiding corrosion of the vessel, which is described in detail in Section 15. Pfaudler and De Dietrich are two suppliers for

pharmaceutical-grade glass lined vessels, and both offered comparable equipment; De Dietrich was selected as the supplier as specifications for the vessel were more readily available. The batch size was selected by considering the required vessel capacity for the following solvent swap step, which requires extra empty volume for ethanol to be added. Glass-lined vessels were available from De Dietrich for working volumes ranging from 63 to 40000 L. Preliminary modeling on Aspen showed that to produce at least 100 kg of API per batch, the minimum working volume required was 2500 L. To maximize profits, the next largest De Dietrich vessel, with 4000 L working volume, was selected so that more API could be produced per batch with a comparatively small capital cost increase. Furthermore, the larger vessel was expected to be more robust for use in other pharmaceutical processes, a key requirement of this process design.

The reaction process is as follows. First, 2042 kg of THF is pumped into the reaction vessel (R-100a) at 20° C. Jacket fluid is heated to 60° C and circulated at 2.20 kg/s to heat the THF to 50° C over 0.77 hours. A De Dietrich Powder Pump, P-101, is then used to transfer 200.33 kg of starting material (SM) in powder form into reaction vessel, where it is dissolved in the THF. The agitator is spun at 50 rpm to aid with heat transfer and achieve homogeneity. After the reaction is completed, 200 kg of product are produced, and 0.38 kg of unreacted SM remain in solution.

13.3 Distillation

After the reaction is completed, the THF must be switched to the crystallization solvent, ethanol (R-100b). The solvents are swapped by continuously adding ethanol to the vessel as the contents are evaporated, allowing the bottoms remaining in the vessel to become concentrated in ethanol. Although the following process may be better described as an evaporation, it will be denoted as a distillation process because it involves the separation and eventual switch of solvents. At the end of the distillation, the desired composition for the solvent remaining in the vessel is

99.5 mole percent of ethanol. It is also desired that the concentration of the API after solvent swap is close to the saturation concentration. Assuming an operating pressure of 1.1 bar, the temperature of the vessel contents at the end of the solvent swap will be 80.5 °C, the boiling temperature of ethanol at 1.1 bar. At 80.5 °C, the solubility of the API in ethanol is 82.2 mg/ml. Based on this, the final volume of the solvent at the end of the distillation was chosen to be 2500 L, at which point the concentration of the API is 80.4 mg/ml. Reduction of temperature during the crystallization step achieves the saturation level required. Furthermore, the API must always remain solvated in the solution throughout the distillation, again to prevent fouling and uncontrolled precipitation.

The solubility data as well as the effect of solvating the API on the thermodynamic properties of the ethanol-THF mixture was unknown. Therefore, key simplifications were needed to model the distillation process. First, it was assumed that the presence of API in the solution does not alter the thermodynamic properties of the mixture, such as the bubble point temperatures, and has zero vapor pressure. Second, the API has negligible vapor pressure; in other words, no API ends up in the distillate. Third, the solubility of the API in ethanol at a given temperature was assumed to be always greater than the solubility in THF. Finally, the solubility of the API in the ethanol-THF mixture was assumed to be at least as great as the solubility of the API in the same total quantity of pure ethanol and THF individually. The first two assumption allowed the distillation to be modelled as a simple swap between ethanol and THF. The latter two assumptions were used to confirm that the API remains soluble in the vessel throughout the distillation process.

The distillation process is as follows. Ethanol is added to the vessel (R-100b) at a rate of 2340 kg/hr for 0.5 hours, which results in a total volume of 4000 L in the vessel. This serves two purposes. First, the vessel is filled to its working capacity to maximize the heat transfer area.

Second, the mixture of ethanol and THF at 1 bar form a low boiling azeotrope at 65.5 °C when the mole fraction of THF is 0.85, as shown in Figure 11.1.1. As such, distillation to concentrate the bottoms in ethanol is not possible when the mole fraction of THF exceeds 0.85. To "jump" the azeotrope and move to the conditional swap region on the left side of the azeotrope, an initial batch of ethanol is added to the reaction vessel such that the mole fraction of THF is lowered below 0.85. The mole fraction of THF inside the vessel following the initial addition is 0.64. The agitator is spun at 50 rpm throughout the distillation process to achieve homogeneity and to improve heat transfer.

The vessel contents are then heated to 68.5 °C, the bubble point of the THF-ethanol mixture with THF mole fraction of 0.64 at 1.1 bar. Jacket fluid is heated to 102 °C and circulated at a mass flow rate of 3.7 kg/s to provide heating. After the reactor contents begin to boil, ethanol is added at 410 kg/hr over 14 hours, for a total of 5742 kg of ethanol. In total, 6913 kg of ethanol are added throughout the distillation; based on ASPEN simulations, the desired final solvent composition of 0.995 mole percent of ethanol could only be reached when at least 6910 kg of ethanol were added (Refer to Section 25.4). The time frame of ethanol addition, and thus the rate of ethanol added, was largely a function of the heat duty that could be applied to the reactor using the jacket fluid. The calculations are described in detail in Section 25.2. After 14 hours of continuous ethanol addition, the remaining solvent is distilled for 4.5 hours until 2500L of solvent remain. At the end of the distillation step, 1817 kg of ethanol and 12.1kg of THF remain in the reaction vessel, corresponding to 0.995 mole percent ethanol in the solvent, and 200. kg of product and 0.38 kg of unreacted SM remain dissolved in the solvent. Aspen simulations were used to confirm that the total volume of the solution did not exceed the maximum capacity of the vessel and that there was always enough volume to keep the API soluble. The minimum mass of API that would be soluble

in the reactor was calculated to be approximately 250 kg, far exceeding the 200. kg of API actually present in the reactor.

13.4 Crystallization

Following distillation, crystallization is employed in the last major step of the process (R-100c). The goal of crystallization is to maximize the amount of product collected and minimize the product lost to the mother liquor. Common methods for pharmaceutical crystallization processes include using an in-situ seeding system or dry-seeding. Dry seeding is chosen as the primary method because an in-situ seeding system, such as a high shear homogenizer, would require the purchase of a new system to complete the crystallization. The dry seeding method would allow for crystallization to occur in the same vessel as the reaction and distillation steps, allowing for economic savings. The dry seeding method uses some of the final product to drive nucleation growth and generate crystals. The amount of dry seed added was 1% of the final product desired, a value commonly used in the pharmaceutical industry [9]. Therefore, 1 kg of dry seed was added into to the reaction vessel. The dry seed is sourced from the research and development facilities for Halfaxia and is safely inserted into the vessel via a split butterfly valve. Further details on the safe handling of the dry seed and ways to minimize exposure are discussed in Section 20.

A key component of this crystallization process is establishing supersaturation, or creating a solution that contains more of the dissolved API than could be dissolved by ethanol under normal circumstances. The temperature of the contents after distillation was 80.5 °C while the minimum supersaturation temperature of the API in ethanol was determined to be 79 °C using crystallization data. The desired supersaturation temperature was set to 77 °C to go beyond the threshold of supersaturation without prematurely precipitating the product. Jacket fluid at 70 °C is circulated at a rate of 3.9 kg/s for 0.30 hours to cool the vessel contents to 77 °C. The dry seed is added after

the supersaturation temperature is achieved. The contents are maintained at 77 °C for 3 hours in order to initiate crystallization by circulating jacket fluid at 77 °C at a rate of 1 kg/s. Because the crystal size and growth rate data are unavailable, the following guidelines from J&J are used: the vessel contents are cooled to the final temperature at a rate of 5 °C per hour. In order to minimize the final product lost to the mother liquor, the final temperature was set for 12 °C, when the solubility of the API is 6.9 mg/ml. This temperature was determined assuming chilled water at 5 °C would be available at the facility for cooling the jacket fluid. A lower temperature could be achieved with refrigerants such as propane and an additional heat exchanger, but this option was not explored in this report.

To control the temperature drop during each hour of crystallization, the jacket fluid temperature is decreased every hour, starting at 69 °C and ending at 7 °C. The jacket fluid is circulated at 1 kg/s for the remainder of the crystallization. The final 5 °C drop between 17 °C and 12 °C with jacket fluid temperature at 7 °C takes 2 hours instead of 1 hour due to the low heat transfer coefficient between the jacket fluid and vessel contents. Detailed calculations for the heat transfer coefficient and heat duty are described in Section 25. A total of 184 kg of API is crystallized, while 17.1 kg of API and 0.38 kg leftover starting material remain dissolved in the solution. The resulting slurry is then sent to the filter-dryer system for separation of the crystallized API from the mother liquor. Because the filter-dryer will be located on the lower floor and the main vessel is on the upper flow of the facility, gravity is used to transfer the slurry to FD-100. Additional information on facility design is described in Section 20.

13.5 Filter Dryer

It is important to note the order of operations for the process streams described so far. Following reaction and distillation steps, the contents of the vessel undergo crystallization after

the addition of the dry seed to the vessel. The vessel contents are cooled to 12 °C and sent to the filter dryer. The filter dryer is a separate piece of equipment from the reaction vessel, shown in Figure 12.1.1 as FD-100. This filter dryer must be able to perform both filtration and vacuum drying; and the De Dietrich's Agitated Nutsche Filter Dryer was preselected to accomplish this step. The objective of this step is to filter out the ethanol in the slurry, leaving behind pure API which must then be dried under a vacuum. Following this step, the API is in powder form, and is ready to be packed into 55-gallon drums and transported.

The method of filtration is Nutsche filtration, which is batch filtration performed in a vacuum and a closed vessel. Nutsche filtration has the advantage of minimizing operator handling and exposure, which is crucial to the design of the process and facility. The slurry (183.9 kg of crystallized API in 1816.8 kg of ethanol) from the reaction vessel is transferred to the filter dryer and subjected to pressure under a vacuum. The ethanol is filtered out through the filtering cloth, leaving behind a cake of API and residue ethanol. The process is repeated until only the API is remaining. An additional rewashing step is be performed by spraying cold ethanol through the spray balls equipped in the filter dryer. After the initial filtering, 145.06 kg of 20 °C ethanol enter the reaction vessel (R-100c) through the spray balls and is cooled to a desired temperature of 12 °C using the jacket fluid and E-101. This fresh ethanol serves to clean the sides of the vessel and recover any loss product [9]. Once the ethanol is properly cooled it is sent to the filter dryer to wash the cake of product that has accumulated and remove any impurities.

A Nutsche filter dryer can accommodate both filtration and drying in the same vessel, eliminating costs for purchasing and installing a separate dryer. Following filtration, the API is vacuum dried to remove any additional moisture residing on the powder. Drying in a vacuum lowers the temperature needed for ethanol to evaporate. This method is highly effective, leaving

behind only 0.1% moisture in the final product [10]. The product is deposited in a tray at the bottom of the equipment, and using another De Dietrich Powder Pump (P-106), it can be transferred safely to 55-gallon drums without operator handling. There will be no physical contact between the operator and the API throughout the entire filtration and drying process.

Exact lengths of duration of filtration and drying are difficult to determine without performing lab-scale experiments. In addition, since the particle size, porosity, and identity of the API are confidential, it is not possible to model this process and determine how long these steps will take. As an approximation, J&J recommended filtering for 6 hours followed by 24 hours of drying.

13.6. Jacket and Heat Exchanger System

A jacket comes installed on the De Dietrich AE-4000 (R-100), with a total heat transfer area of 11.7 m^2 and capacity of 499 L. The fluid in the jacket is circulated to heat or cool the vessel contents, as described in Sections 13.1 to 13.4. The flow rates and temperature of the jacket during the production process, which change frequently depending on the desired vessel content temperature, are shown in Tables 12.2.2, 12.2.3, and 12.2.4. The heat transfer coefficient between the jacket and vessel ranges between 330 and 65 W/m^2-K depending on jacket flow characteristics and vessel contents. The derivation of the flow rates and temperature were dependent on the required heat duty, which is described further in Section 14.1.

The temperature of the jacket fluid is controlled by one steam heat exchanger (E-100) and one water heat exchanger (E-101), both simplified as a shell-and-tube heat exchanger. Separate heat exchangers are required because the distillation process involves fast heating by making use of the high temperature of steam, while incremental heating and cooling is also necessary to

maintain the vessel temperature and to facilitate a controlled drop in temperature during the crystallization.

The steam heat exchanger has a heat transfer area of 6 m^2 and is designed for use with steam on the shell-side. A valve on the steam inlet is used to alter the steam pressure, and therefore the steam temperature, in order to control the rate of heat transfer between the jacket fluid and the steam. Steam temperatures range between 106 °C and 144 °C, corresponding to pressures of 3.5 psig to 50 psig. Steam is assumed to be available at the facility form a separate water boiler.

The second heat exchanger has a heat transfer area of 10 m^2 and is designed for use with water on the shell-side. Depending on the temperature of jacket fluid required for each process step, the temperature of water ranges from 83 °C to 5 °C. All water is assumed to be available at the facility from either a separate water heater or cooling tower.

The activated time period for each heat exchanger, as well as the flow rate and temperature of the heating or cooling utility, was dependent on the energy requirements. The flow rate and temperature of the utility for all operational steps are described in Section 14.1 in Tables 14.1.1 to 14.1.3. The sizing and utility requirement calculations for the heat exchangers are further described in Section 25.2.5 of the Appendix.

Depending on the flow rate, the jacket fluid takes approximately 3 to 5 minutes to change temperature by passing through the heat exchangers and be recirculated into the jacket. For each operational step that involves a temperature change in the vessel, the temperature of the jacket fluid is changed approximately 3 to 5 minutes before the end of the previous step such that the jacket fluid with the changed temperature reaches the jacket right as the next operational is scheduled to begin.

13.7. Condenser

The condenser was simplified as a shell-and-tube heat exchanger with a heat transfer area of 6 m^2. The condenser was operated only during the distillation step to condense the vapor from the reaction vessel, totaling 18.50 hours of operation. The vapor flows through the shell side as it is the condensing fluid, while the cooling water flows through the tube side. The vapor, which changes in temperature and composition throughout the distillation, is condensed using 20 °C cooling water flowing at 6500 kg/hr. The heat transfer area and cooling water flow rate were chosen to accommodate the greatest heat duty required. The sizing and utility requirement calculations are further described in Section 25.2. The resulting distillate, containing 2030 kg of THF and 5096 kg of ethanol per batch, is stored in waste tank W-100 and subsequently disposed of, as described in Sections 13.9 and 20.

13.8 Pumps

Pumps are used throughout this process to overcome frictional forces and transfer fluid from one area to another. This design must be capable of handling several different pharmaceutical processes, therefore the pumps followed design guidelines of 30 m of head loss or a pressure drop of 3 bar. These guidelines were used for more detailed design of the pumps as described in Section 15 of the report. P-100 and P-104 represent pumps to move THF and ethanol from storage tanks into the main vessel. P-101and P-106 are specialty powder pumps provided by De Dietrich that can transfer the solid starting material (A) and the API product in a safe and contained manner. P-102 serves as the heat exchanger pump to move 30% w/w ethylene glycol at the desired flow rate through the jacket and heat exchangers. P-103 and P-105 serve as waste pumps to transfer the distillate and mother liquor into each waste tank respectively. The pumps used throughout this

process serve as a critical tool for automating the process and minimizing exposure for the operators.

13.9 Storage and Waste Tanks

Storage tanks are used to hold the solvents THF and ethanol before they are transferred via pump to the reaction vessel, and waste tanks are used to hold the distillate from the distillation step and the mother liquor from the crystallization step. One batch will require 7058 kg of ethanol (8945 liters) and 2042 kg of THF (2298 liters), and it will generate 7126 kg of distillate waste (8744 liters) and 1846 kg of mother liquor (2389 liters). Thus, the storage and waste tanks must be appropriately sized to hold the necessary amount required or generated per batch and for future batches so that the materials do not have to be constantly replenished or removed from the site with each batch. The compounds in the pressure vessel must be kept at atmospheric pressure; THF and ethanol will be kept at room temperature prior to production.

Guidelines for sizing storage tanks and pressure vessels can be found in Chapter 16 of Seider et al. et. al. The storage tanks are designed as horizontal pressure vessels constructed from carbon steel and can be held inside the facility next to the reaction vessel. Tables 25.2.7.1 and 25.2.7.2 in the Appendix show the design calculations to determine the volume and size of the pressure vessels corresponding to the amount of material required or generated to make three batches of API, which take approximately a week to produce. This will allow tanker trucks to come once every week to replenish THF and ethanol while removing distillate and mother liquor.

Two 28,391-liter tanker trucks (7500 gallons) will come to the facility once a week to pick up distillate waste and supply fresh ethanol, and two 9464-liter tanker trucks (4000 gallons) will pick up the mother liquor as waste and supply fresh THF. Seider et al. et. al recommends that storage tanks be sized at least 1.5 times the size of the vehicles used to transport the materials;

thus, the horizontal pressure vessels for ethanol and the distillate waste will be 45,425 liters each (standard size of 12,000 gallons), while the vessels for THF and mother liquor will be 15,142 liters each (standard size of 4,000 gallons). The horizontal pressure vessels will be constructed using stainless steel, which will prevent corrosion and maintain the sterility of the materials. A potential pressure vessel company that offers suitable vessels is Highland Tank and Manufacturing Company, Inc.

The API in powder form will be packed in 55-gallon stainless steel drums. The drums will be picked up by trucks and transferred to a milling facility where the API will be processed further into drug form. The milling process and design of these stainless steel drums is out of scope of our project.

Section 14: Energy Balance and Utility Requirements

14.1 Process Requirements for Operational Steps: Vessel Jacket and Heat Exchangers

Throughout the API production process, the contents of the vessel (R-100) need to be heated and cooled numerous times. To do so, 30% w/w ethylene glycol is circulated through the jacket at varying flow rates and temperatures depending on the operational step. The temperature difference between the jacket and vessel contents drives the rate of heat transfer, while the flow rate controls the overall heat transfer coefficient and the amount of heat that can be transferred. Because the flow rate affects both the amount of heat transfer that can be transferred and the heat transfer coefficient, which are also interrelated, an iterative process was used to ensure that the selected flow rate of the jacket provides the correct amount of heat to be transferred and the correct overall heat transfer coefficient. The heat transfer coefficient between the jacket and vessel ranged between 330 and 65 W/m^2-K depending on jacket flow characteristics and vessel contents. The calculations are described in detail in Section 25.2.4 and 25.2.5.

After exiting the jacket, the jacket fluid is circulated into one of two heat exchangers (E-100, E-101), which cool or heat the jacket fluid as necessary. Because the temperature of the jacket fluid in contact with the vessel must be kept relatively constant during each operational step, the energy that was exchanged between the jacket and vessel must be reciprocally exchanged between the jacket fluid and the heat exchangers. To accomplish this, different utilities are used on the shell-side of the heat exchangers. Each utility is covered in more detail in Sections 14.2 to 14.5. Overall, four parameters needed to be determined for each operational step to properly account for all heat transfer occurring in the manufacturing process; the temperature and flow rate of the jacket fluid, and the temperature and flow rate of the utility through the heat exchanger. These values are shown in Table 14.1.1 to 14.1.3, which replicates portions of Table 12.1.2 to 12.1.4. The calculations are described in further detail in Appendix 25.2.

Both water and steam heat exchangers and the condenser were sized by finding the required heat transfer area necessary to deliver the maximum heat duty required for the processes involving each heat exchanger. The detailed calculations are described in Section 25.2.6.

Table 14.1.1 Jacket Fluid and Utility Requirements for the Reaction as a Function of Time

Stream Number	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**
Operational Step	*Heat Jacket Fluid from 20 to 60 °C*		Heat *R-100a contents* from 20 to *50 °C*		*Cool Jacket Fluid from 60 to 50 °C*		*Maintain R-100a contents at 50 °C*	
Jacket Fluid Temperature (°C)	20	60	55	60	60	50	49	50
30% w/w Ethylene Glycol (kg/s)	2.20	2.20	2.20	2.20	0.91	0.91	0.91	0.91
Operation Time Per Batch (hr):	0.076		0.77		0.18		6.00	
Average Heat Duty (kJ/hr)	1.15×10^{6}		1.47×10^{5}		-1.20×10^{5}		4.84×10^{3}	
Utility:	lps		hw		hw		hw	
Utility Inlet temperature (°C)	113		71		46		50	
Utility Flow Rate (kg/hr)	524.4		7036.4		5747.1		1157.7	

Table 14.1.2 Jacket Fluid and Utility requirements for Distillation as a Function of Time

Stream Number	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**	**ri**	**ro**
Operational Step	*Heat Jacket Fluid from 50 to 85 °C*		*Heat R-100b contents from 50 to 68 °C*		*Heat Jacket Fluid from 90 to 102 °C*		*Carry out Solvent Swap in R-100b*	
Jacket Fluid Temperature (°C)	50	85	85	90	90	102	97	102
30% w/w Ethylene Glycol (kg/s)	3.45	3.45	3.45	3.45	3.72	3.72	3.72	3.72
Operation Time Per Batch (hr):	0.05		0.51		0.04		18.80	
Average Heat Duty (kJ/hr)	1.15×10^{6}		2.94×10^{5}		6.03×10^{5}		3.29×10^{5}	
Utility:	lps		lps		lps		lps	
Utility Inlet temperature (°C)	148		106		133		120	
Utility Flow Rate (kg/hr)	535.9		131.3		278.9		149.5	

Table 14.1.3 Outline of Jacket Fluid and Utility Requirements for Crystallization as a Function of Time

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Operational Step	*Cool Jacket Fluid from 102 to 70 °C*		*Cool R-100c contents from 80.2 to 77.2 °C*		*Heat Jacket Fluid from 70 to 77 °C*		*Hold R-100c Contents at 77 °C*		*Cool Jacket Fluid from 77 to 69 °C*		*Cool R-100c contents from 77.2 to 72 °C*		*Cool Jacket Fluid from 69 to 64 °C*		*Cool R-100c contents from 72 to 67 °C*	
Jacket Fluid Temperature (°C)	102	70	75	70	70	77	77	78	77	69	71	69	69	64	66	64
30% w/w Ethylene Glycol (kg/s)	1.00	1.00	3.90	3.90	1.06	1.06	1.06	1.06	1.05	1.05	1.05	1.05	1.01	1.01	1.01	1.01
Operation Time Per Batch (hr):	0.17		0.30		0.16		3.00		0.16		1.00		0.16		1.00	
Average Heat Duty (kJ/hr)	-4.30×10^{5}		-5.25×10^{4}		9.95×10^{4}		4.31×10^{3}		-1.13×10^{5}		-2.55×10^{4}		-6.75×10^{4}		-2.45×10^{4}	
Utility:	hw		hw		hw		hw		hw		hw		hw		hw	
Utility Inlet Temperature (°C)	55		67		83		79		64		67		61		62	
Utility Flow Rate (kg/hr)	10293.0		2512.8		4760.5		1031.0		5386.4		6105.9		3228.6		5860.9	

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Operational Step	*Cool Jacket Fluid from 64 to 59 °C*		*Cool R-100c contents from 67 to 62 °C*		*Cool Jacket Fluid from 59 to 54 °C*		*Cool R-100c contents from 62 to 57 °C*		*Cool Jacket Fluid from 54 to 49 °C*		*Cool R-100c contents from 57 to 52 °C*		*Cool Jacket Fluid from 49 to 43 °C*		*Cool R-100c contents from 52 to 47 °C*	
Jacket Fluid Temperature (°C)	64	59	61	59	59	54	56	54	54	49	51	49	49	43	46	43
Pressure (bar)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
30% w/w Ethylene Glycol (kg/s)	1.04	1.04	1.04	1.04	1.05	1.05	1.05	1.05	1.07	1.07	1.07	1.07	1.15	1.15	1.15	1.15
Operation Time Per Batch (hr):	0.16		1.00		0.16		1.00		0.16		1.00		0.14		1.00	
Average Heat Duty (kJ/hr)	-6.88×10^{4}		-2.36×10^{4}		-6.96×10^{4}		-2.25×10^{4}		-7.07×10^{4}		-2.14×10^{4}		-9.10×10^{4}		-2.30×10^{4}	
Utility:	hw		hw		hw		hw		hw		hw		hw		hw	
Utility Inlet Temperature (°C)	56		57		51		49		46		44		39		41	
Utility Flow Rate (kg/hr)	3293.3		5647.1		3328.7		5373.3		3381.5		5118.6		4353.7		5492.4	

Table 14.1.3 (cont.) Outline of Jacket Fluid Temperature for Crystallization as a Function of Time

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Goal	*Cool Jacket Fluid from 43 to 38 °C*		*Cool R-100c contents from 47 to 42 °C*		*Cool Jacket Fluid from 38 to 32 °C*		*Cool R-100c contents from 42 to 37 °C*		*Cool Jacket Fluid from 32 to 27 °C*		*Cool R-100c contents from 37 to 32 °C*		*Cool Jacket Fluid from 27 to 21 °C*		*Cool R-100c contents from 32 to 27 °C*	
Jacket Fluid Temperature (°C)	43	38	41	38	38	32	35	32	32	27	30	27	27	21	24	21
30% w/w Ethylene Glycol (kg/s)	0.93	0.93	0.93	0.93	1.08	1.08	1.08	1.08	1.04	1.04	1.04	1.04	1.05	1.05	1.05	1.05
Operation Time Per Batch (hr):	0.18		1.00		0.15		1.00		0.16		1.00		0.16		1.00	
Average Heat Duty (kJ/hr):	-6.12×10^4		-2.35×10^4		-8.49×10^4		-2.57×10^4		-6.76×10^4		-2.46×10^4		-8.16×10^4		-2.48×10^4	
Utility:	hw		hw		cw		cw		cw		Cw		cw		cw	
Utility Inlet Temperature (°C):	29		30		24		25		18		19		29		30	
Utility Flow Rate (kg/hr)	6771.2		6155.0		5388.1		5881.5		6509.1		5922.1		6771.2		6155.0	

Stream Number	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**	**ci**	**co**
Goal	*Cool Jacket Fluid from 21 to 15 °C*		*Cool R-100c contents from 27 to 22 °C*		*Cool Jacket Fluid from 15 to 9 °C*		*Cool R-100c contents from 22 to 17 °C*		*Cool Jacket Fluid from 9 to 7 °C*		*Cool R-100c contents from 17 to 12 °C*	
Jacket Fluid Temperature (°C)	21	15	18	15	15	9	12	9	9	7	11	7
30% w/w Ethylene Glycol (kg/s)	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.08	1.02	1.02	1.02	1.02
Operation Time Per Batch (hr):	0.15		1.00		0.15		1.00		0.16		2.00	
Average Heat Duty (kJ/hr):	-8.40×10^4		-2.41×10^4		-8.34×10^4		-2.27×10^4		-2.62×10^4		-1.40×10^4	
Utility:	cw		cw		cw		cw		cw		cw	
Utility Inlet Temperature (°C):	10		13		5		7		6		6	
Utility Flow Rate (kg/hr)	6701.8		5762.4		6646.8		5428.7		2092.3		3360.2	

14.2 Total Utility Demands

The total utility demand described in Table 14.2.1 and Table 14.2.2 summarizes the total utility requirements per gram of API produced in one batch. The total amount of API produced in one batch is 184 kg or 184 grams. Details for the cost of each utility are described in Section 17.

Table 14.2.1 Utility Requirements per Batch of Halfaxia Synthesis

Utility	Equipment Used	Quantity
Low Pressure Steam (kg)	E-100	2957
Chilled Water (GJ)	E-101	5317
Hot Water (m^3)	E-101	4402
Cooling Water (m^3)	E-102	8484
Electricity (kWh)	P-100	0.300
	P-101	2.07
	P-102	132.17
	P-103	1.20
	P-104	1.58
	P-105	0.332
	P-106	1.94
	R-100a-c (agitators)	52.72
	FD-100	502.5

Table 14.2.2 Total Utility Requirements per Gram of Halfaxia API in one Batch

Utility	Unit	Ratio (per gram Halfaxia)
Low Pressure Steam	kg	0.016
Chilled Water	GJ	0.029
Hot/Cooling Water	m^3	0.070
Electricity	kWh	0.0038

14.3 Low Pressure Steam

Low pressure steam is used throughout this process in E-100 heat up the 30% w/w ethylene glycol jacket fluid. Details on when steam is used is shown in Tables 12.2.2, 12.2.3, and 12.2.4. Guidelines from *Product and Process Design Principles* suggest low pressure steam should operate at 50 psig and 148 °C. However, the use of a single heat exchanger to handle different heat duties creates variations in the temperature and pressure of the steam. As described in Section 13.6, steam temperatures range between 106 °C and 144 °C, corresponding to pressures of 3.5 psig to 50 psig. The heat duty required for each steam heating process coupled with the latent heat of vaporization provides the mass flow rate of steam required for each process. The time of operation for each steam flow rate was used to calculate the total mass of steam required for each batch.

14.4 Chilled Water

Chilled water is required in E-101 to cool the jacket fluid to temperatures below 32 °C for crystallization, which is highlighted in Table 12.2.4. It is important to note that the refrigeration unit will be co-located with this process and does not need to be designed as part of the cost. Following Chapter 17 of Seider et al., the chilled water requirements were calculated by converting the cooling duty to tons using the heat of removal to freeze one ton per day of water, which corresponds to 12,000 BTU/hr. The quantity in of tons was converted to ton-days using the operating factor for the plant, 0.9041 (described in Section 19), and the total time of operation for the chilled water. The ton-days were converted to GJ to stay consistent with metric units. Therefore, 5317 GJ of chilled water are required per batch of API synthesis.

14.5 Cooling and Hot Water

Hot water is used in E-101 to heat up the 30% w/w ethylene glycol jacket fluid described in Section 12 of the report. Cooling water is used in E-102 to condense the distillate leaving R-100b. Although hot water is not a typical utility mentioned in *Product and Process Design Principles,* this process requires water at temperatures above 50 °C. For both the hot and cooling water, the heat capacity and temperature change of the water were used with the heat duty of the process to calculate the flow rate of water required. The cooling and hot water requirements are listed together in Table 14.2.2 because it is assumed that they have the same cost. The cooling and hot water demand is 0.070 kg/gram of Halfaxia.

14.6 Electricity

The components that use electricity in this process are the agitators in R-100a-c, the filter dryer (FD-100), and all of the pumps (P-100, P-101, P-102, P-103, P-104, P-105, P-106). Using detailed specification sheets mentioned in Section 25.4 of the Appendix, the AE 4000 vessel has a motor power of 7.5 kW. Additionally, the filter dryer has electricity requirements of 16.75 kW. Each electricity requirement was multiplied by the time of unit operation, 7.03 hours for the reaction and 32 hours for filter drying to convert to kWh. The electricity requirements for P-100, P-102, P-103, P-104, and P-105 are described in detail in section 25.2.3 of the Appendix and Section 15.3. Each pump's horsepower was converted to kWh using the time of operation. For the specialty powder pumps, P-101 and P-106, detailed specification sheets from De Dietrich revealed a motor power of 5 hp per pump. Similarly, this power was converted to kWh using the time of operation for each powder pump. The total electricity required per batch is 695 kWh.

Section 15: Equipment List and Unit Descriptions

15.1 Main Vessel

De Dietrich AE 4000 Vessel: R-100a-c

Unit ID: R-100a-c	Capacity: 4000 L (Working)
Type: Reaction, Distillation, Crystallization Vessel	Diameter: 1.9 m (including jacket)
Material: Glass-Lined Stainless Steel	Agitator Length: 0.750 m
Specification Sheet: Section 16	Additional Features: spray nozzles, agitators
Costing Data: Section 17	Design Details: Section 25.4

The De Detrich AE 4000 Vessel is the main component of this pharmaceutical process. It has a working capacity of 4000 L with a diameter of 1.9 m including the jacket. The material of construction is glass lined stainless steel due to the corrosive nature of the API product and starting material that can deteriorate the lining of the vessel. This vessel was chosen following recommendations by industrial consultants and considering standard pharmaceutical industry equipment. The vessel cost and specifications were taken directly from quotes from the company De Dietrich. The purchase cost of this equipment is $220,000. Section 16 provides additional specification for the vessels during the reaction, distillation, and crystallization steps. Additionally, Section 25.4 contains detailed specification sheets from the manufacturer.

The overall heat transfer coefficient of between the vessel and jacket is dependent on the flow characteristics and thermodynamic properties of the vessel contents and jacket fluid, as well as the properties of the stainless steel wall and glass lining. For the conditions applied during this manufacturing process, the overall heat transfer coefficient ranged between 330 and 65W/m^{2-}K. Calculations are described in Section 25.2.

15.2 Filter Dryer

De Dietrich Nutsche Filter Dryer

Unit ID: FD-100	Capacity: 4660 L
Type: Filter Dryer	Diameter: 2.3 m
Material: Glass-Lined	Agitator Length: 0.400 m
Specification Sheet: Section 16	Additional Features: spray nozzles, agitators, universal filter media, high containment discharge isolator
Costing Data: Section 17	Design Details: Section 25.4

The De Dietrich Nutsche Filter Dryer is the filter dryer (FD-100) for this process. This specific brand was chosen based on recommendations from industrial consultants and pharmaceutical industry standards for containment and safety. It has a total volume of 4660 liters, a usable volume of 3720 liters, and a filtration surface of 4.08 m^2 following detailed specification sheets in Section 25.4. The material of construction is glass-lined stainless steel for corrosion resistance against the hazardous API product. Alternate materials such as Hastelloy were considered for the material of construction, however the De Dietrich manufacturer only provides glass lined stainless steel. This filter dryer has a rigid discharge glovebox specifically built to handle highly potent material and reduces the need for personal protective equipment. It will be equipped with spray balls to wash the contents with fresh ethanol. Stream 10 from R-100c will enter FD-100. Stream 12 will leave FD-100 with the product, while the mother liquor will leave and enter waste tank W-101.

15.3 Heat Exchangers

Steam Heat Exchanger: E-100

Unit ID: E-100	Max Heat Duty: 1.15×10^6 kJ/hr
Type: Heat Exchanger	Min Heat Duty: 2.94×10^5 kJ/hr
Material: Stainless Steel	Heat Transfer Area: 6 m^2
Specification Sheet: Section 16	Utility Used: Steam
Costing Data: Section 17	Design Calculation: Section 25.2.5

The steam heat exchanger (E-100) is a shell-and-tube heat exchanger with a heat transfer area of 6 m^2. Steam of varying temperatures and pressures are flown through the shell side, while the jacket fluid is flown though the tube side. The overall heat transfer coefficient was estimated to be 750 W/m^2-K. The steam heat exchanger serves to provide heat to the jacket fluid for reaction and distillation operational steps requiring a high heat duty. Constructed from stainless steel, the heat exchanger has a fixed head. The tube length was assumed to be 2.4 m of tube length for costing purposes. Detailed design calculations are found in Section 25.2.5.

Water Heat Exchanger: E-101

Unit ID: E-101	Max Heat Duty (Heating): 9.95×10^4 kJ/hr Min Heat Duty (Cooling): 4.31×10^3 kJ/hr
Type: Heat Exchanger	Max Heat Duty (Heating): -1.13×10^5 kJ/hr Min Heat Duty (Cooling): $-1.4.0 \times 10^4$ kJ/hr
Material: Stainless Steel	Heat Transfer Area: 10 m^2
Specification Sheet: Section 16	Utility Used: Hot and Chilled Water
Costing Data: Section 17	Design Calculation: Section 25.2.5

The water heat exchanger (E-102) is a shell-and-tube heat exchanger with a heat transfer area of 10 m^2. Water of varying temperatures are flown through the shell-side, while the jacket fluid is flown through the tube side. The water heat exchanger serves to provide heat to the jacket fluid for operational steps requiring a comparatively smaller heat duty. Constructed from stainless steel, the heat exchanger has a fixed head. The tube length was assumed to be 2.4 m of tube length for costing purposes. Detailed design calculations are found in section 25.2 of the Appendix.

Distillate Condenser: E-102

Unit ID: E-102	Max Heat Duty: -404,009 kJ/hr
Type: Heat Exchanger	Heat Transfer Area: 6 m^2
Material: Stainless Steel	Utility Used: Cooling Water
Specification Sheet: Section 16	Design Calculation: Section 25.2.5
Costing Data: Section 17	

The distillate condenser (E-102) is a shell-and-tube heat exchanger with a heat transfer area of 10 m^2. Cooling water is flown through the tube side, while the distillate vapor is flown through the shell side. The water heat exchanger serves to provide heat to the jacket fluid for operational steps requiring a comparatively smaller heat duty. Constructed from stainless steel, the heat exchanger has a fixed head. The tube length was assumed to be 2.4 m of tube length for costing purposes. Detailed design calculations are found in section 25.2.5.

15.3 Pumps

All of the pumps used in this process serve the same function of overcoming frictional forces to move fluid from one area to another. Therefore, all pumps followed similar approaches to the design calculations explained in Section 25.2.3. In order to avoid complex frictional calculations and to maintain a general flexibility for this process, the pumps are designed with the approximations of 3 bar pressure loss, 100 ft of head loss, and 1,800 shaft rpm. These guidelines provided by industrials consultants aid in more detailed calculations for each pump. Additionally, the total electricity required for each pump's electric motor is found by converting the work into kWh using each time of operation. For all pumps except for P-101 and P-106, stainless steel was chosen as the material of construction to maintain cleanliness and avoid corrosion, which are typical attributes for pharmaceutical processes.

THF Pump: P-100

Unit ID: P-100	Head: 35 m
Type: Pump	Pressure Change: 3 bar
Material: Stainless Steel	Work:14.08 hp
Specification Sheet: Section 16	Flow Rate: 20 L/s
Costing Data: Section 17	Design Calculation: Section 25.2.3

P-100 is a centrifugal pump that transfers fluid from storage tank T-100 into vessel R-100a. The flow rate of the pump, 20 L/s, was chosen based on the need to move 2042.29 kg of THF per batch in an appropriate amount of time. The purchase cost of the pump and electric motor is $17,53 as described in Section 17.

Starting Material Powder Pump: P-101

Unit ID: P-102	Head: 15.24 m
Type: Pump	Height: 0.82 m
Material: Hastelloy	Work: 5 hp
Specification Sheet: Section 16	Additional Features: PLC Control Panel, valves
Costing Data: Section 17	Design Details: Section 25.4

P-101 is a specialty powder pump from De Dietrich, the same manufacturer of the main vessel used in this process. This pump serves to transfer the solid power starting material from T-100 into the main reaction vessel, R-100a. The pump ensures the transfer is controlled, contained, and capable of minimizing exposure between the operators and the toxic starting material. This pump follows design guidelines from the manufacturer, with a head loss of 15.24 meters and a work requirement of 5 hp. The material of construction is Hastelloy, which has high purity and excellent corrosion resistance for the hazardous starting material. The purchase cost of the pump and electric motor is $35,000 as described in Section 17.

Jacket Fluid Pump: P-102

Unit ID: P-102	Head: 28.11 m
Type: Pump	Pressure Change: 3 bar
Material: Stainless Steel	Work: 4.11 hp
Specification Sheet: Section 16	Flow Rate: 4 L/s
Costing Data: Section 17	Design Calculation: Section 25.2.3

P-102 is a centrifugal pump used to move 30% w/w ethylene glycol through the required heat exchangers and the jacket of R-100a-c. The pump allows for the circulation of 30% w/w ethylene glycol at the desired flow rates that are specified in Tables 12.2.3 to 12.2.4. Because the flow rates of ethylene glycol vary significantly based on the required heating or cooling process, a maximum flow rate of 4 L/s was used in the design calculation to accommodate changing rates. The specification sheet in section 16 does not specify the exact flow rates and temperatures of the fluid, as this is described in detail in Tables 12.2.2 to 12.2.4. The purchase cost of the pump and electric motor is $14,467 as described in Section 17.

Distillate Pump: P-103

Unit ID: P-103	Head: 38.1 m
Type: Pump	Pressure Change: 3 bar
Material: Stainless Steel	Work: 8.05 hp
Specification Sheet: Section 16	Flow Rate: 10 L/s
Costing Data: Section 17	Design Calculation: Section 25.2.3

P-103 is a centrifugal pump that transfers condensed fluid from E-102 into waste tank W-100. The flow rate, 10 L/s, was chosen to move 7126.41 kg of distillate in an appropriate amount of time. Because the distillate contains a mixture of ethanol and THF, appropriate weighted density properties were used to calculate the head loss of 38.1 m. The purchase cost of the pump and electric motor is $15,251 as described in Section 17.

Ethanol Pump: P-104

Unit ID: P-104	Head: 39 m
Type: Pump	Pressure Change: 3 bar
Material: Stainless Steel	Work: 3.49 hp
Specification Sheet: Section 16	Flow Rate: 3.15 L/s
Costing Data: Section 17	Design Calculation: Section 25.2.3

P-104 is a centrifugal pump that transfers ethanol fluid from T-101 into vessel R-100b for the solvent swap stage in this process. The flow rate, 3.15 L/s, was chosen to move 6913.01 kg of ethanol in an appropriate amount of time. The purchase cost of the pump and electric motor is $14,346 as described in Section 17.

Mother Liquor Pump: P-105

Unit ID: P-105	Head: 38.78 m
Type: Pump	Pressure Change: 3 bar
Material: Stainless Steel	Work: 9.66 hp
Specification Sheet: Section 16	Flow Rate: 12.6 L/s
Costing Data: Section 17	Design Calculation: Section 25.2.3

P-105 is a centrifugal pump that transfers the mother liquor into the waste tank W-101. The flow rate, 12.6 L/s, was chosen to move 1991.42 kg of mother liquor in an appropriate amount of time. The mother liquor assumed properties of ethanol when calculating the head loss. The purchase cost of the pump and electric motor is $15,911 as described in Section 17.

API Product Powder Pump: P-106

Unit ID: P-102	Head: 15.24 m
Type: Pump	Height: 0.82 m
Material: Hastelloy	Work: 5 hp
Specification Sheet: Section 16	Additional Features: PLC Control Panel, valves
Costing Data: Section 17	Design Details: Section 25.4

P-106 is a specialty powder pump from De Dietrich, the same manufacturer of the main vessel used in this process. This pump serves to transfer the solid API product from the filter dryer (FD-100) into 55-gallon drums that are outside the scope of this project. The pump ensures the transfer is controlled, contained, and capable of minimizing exposure between the operators and the toxic starting material. This pump follows design guidelines from the manufacturer, with a head loss of 15.24 meters and a work requirement of 5 hp. The material of construction is Hastelloy, which has high purity and excellent corrosion resistance for the hazardous API product. The purchase cost of the pump and electric motor is $35,000 as described in Section 17.

15.4 Storage and Waste Tanks

Ethanol Storage Tank

Unit ID: T-101	Total Volume: 45,425 L
Type: Horizontal Pressure Vessel	Diameter: 2.74 m
Material: Stainless Steel 304	Length: 7.32 m
Specification Sheet: Section 16	Additional Features: Wind/Earthquake protection
Costing Data: Section 17	Design Calculation: Section 25.2.7

The ethanol storage tank (T-101) is a horizontal pressure vessel that will contain 26,835 liters of fresh ethanol for use in the production of three batches. New ethanol will replenish the pressure vessel once each week. T-101 will feed into Pump P-104 and will supply ethanol to R-100b during distillation (Stream 4). T-101 will also feed into R-100c during the final wash step of filtration (Stream 8). It will be maintained at atmospheric pressure and at 20 °C.

THF Storage Tank

Unit ID: T-100	Total Volume: 15142 L
Type: Horizontal Pressure Vessel	Diameter: 1.83 m
Material: Stainless Steel 304	Length: 5.49 m
Specification Sheet: Section 16	Additional Features: Wind/Earthquake protection
Costing Data: Section 17	Design Calculation: Section 25.2.7

The THF storage tank (T-101) is a horizontal pressure vessel that will contain 6893 liters of fresh THF for use in the production of three batches. New THF will replenish the pressure vessel once each week. T-100 will feed into Pump P-100 and will supply THF to R-100a during distillation (Stream 1). It will be maintained at atmospheric pressure and at 20 °C.

Distillate Waste Tank

Unit ID: W-100	Total Volume: 45,425 L
Type: Horizontal Pressure Vessel	Diameter: 2.74 m
Material: Stainless Steel 304	Length: 7.32 m
Specification Sheet: Section 16	Additional Features: Wind/Earthquake protection
Costing Data: Section 17	Design Calculation: Section 25.2.7

The distillate waste tank (W-100) is a horizontal pressure vessel that will contain 26,233 liters of distillate waste from the distillation step generated in the production of three batches. Collected distillate waste will be disposed of once each week. The distillate from R-100b will feed into Pump P-103 and into W-100 (Stream 6). It will be maintained at atmospheric pressure and at 20 °C.

Mother Liquor Storage Tank

Unit ID: W-101	Total Volume: 15142 L
Type: Horizontal Pressure Vessel	Diameter: 1.83 m
Material: Stainless Steel 304	Length: 5.49 m
Specification Sheet: Section 16	Additional Features: Wind/Earthquake protection
Costing Data: Section 17	Design Calculation: Section 25.2.7

The mother liquor waste tank (W-101) is a horizontal pressure vessel that will contain 7166 liters of mother liquor from the crystallization step generated in the production of three batches. Collected mother liquor will be disposed of once each week. The waste from R-100c will feed into Pump P-105 and into W-101. It will be maintained at atmospheric pressure and at 20 °C.

Section 16: Specification Sheets

Note: R-100a, R-100b and R-100c refer to a single piece of equipment. Various spec sheets shown for each step to highlight differences in heat transfer area and materials handled.

Batch API Process: Reaction Vessel

Identification:	**Item**	*Reaction Vessel*	Date: 21 April 2020
	Item No.	R-100a	By: ACL
	No. Required	1	

Function: Carry out reaction of starting material in THF to create API product

Operation: Batch

Materials Handled	*1*	*2*	*3*
Temperature (°C)	20	20	50
Pressure (bar)	1	1	1
Mass (kg)	2042.29	200.33	2242.62
Component Mass (kg)			
THF	2042.29	0	2042.29
Ethanol	0	0	0
Starting Material	0	200.33	0.38
Product	0	0	199.95
Dry Seed	0	0	0
30% w/w Ethylene Glycol	0	0	0

Design Data:

Vessel Volume: 4000 L
Jacket Volume: 560 L
Heat Transfer Area: 7.02 m^2
Average Heat Transfer Coefficient: 210 W/m^2-K
Inner Diameter of Vessel: 1.8 m
Diameter Including Jacket: 1.9 m
Jacket inlet nozzle diameter: 52.5mm
Agitator Length: 0.750 m
Agitator Speed: 50
Material of Construction: Glass Lined Stainless Steel
Thickness of Lining: 1.5 mm
Thermal Conductivity of Lining: 1 W/m-K
Thickness of Wall (Stainless Steel): 20 mm
Thermal Conductivity of Wall: 40 W/m-K
Vessel Temperature: 50 °C
Vessel Pressure: 1.1 bar
Company and Name: De Dietrich AE 4000

Utilities per Batch: 52.72 kWh for agitators, see Section 14.2 for additional detail

Comments and Drawings: See PFD in Figure 12.1. Jacket material ignored – Refer to Table 12.2.2. Refer to Section 25.2 for detailed specifications and Section 17 for equipment costs. R100a, R100b, R-100c refer to the same vessel.

Batch API Process: Distillation Vessel

Identification:	**Item**	*Distillation Vessel*	Date:	21 April 2020
	Item No.	R-100b	By:	ACL
	No. Required	1		

Function: Carry out distillation to swap Ethanol for THF

Operation: Batch

Materials Handled	*3*	*4*	*5*	*7*
Temperature (°C)	50	20	80	80
Pressure (bar)	1	1	1	1
Mass (kg)	2242.62	6913.01	7126.41	2029.22
Component Mass (kg)				
THF	2042.29	0	2030.19	12.10
Ethanol	0	6913.01	5096.22	1816.79
Starting Material	0.38	0	0	0.38
Product	199.95	0	0	199.95
Dry Seed	0	0	0	0
30% w/w Ethylene Glycol	0	0	0	0

Design Data:

Vessel Volume: 4000 L
Jacket Volume: 560 L
Heat Transfer Area: 9.95 m^2
Average Heat Transfer Coefficient: 339 W/m^2-K
Inner Diameter of Vessel: 1.8 m
Diameter Including Jacket: 1.9 m
Jacket inlet nozzle diameter: 52.5mm
Agitator Length: 0.750 m
Agitator speed: 50 rpm
Material of Construction: Glass Lined Stainless Steel
Thickness of Lining: 1.5 mm
Thermal Conductivity of Lining: 1 W/m-K
Thickness of Wall (Stainless Steel): 20 mm
Thermal Conductivity of Wall: 40 W/m-K
Vessel Temperature: 50 to 80 °C
Vessel Pressure: 1 bar
Company and Name: De Dietrich AE 4000

Utilities per Batch: See section 14.2 for additional detail

Comments and Drawings: See PFD in Figure 12.1. Jacket material ignored – Refer to Table 12.2.3. Refer to Section 25.2 for detailed specifications and Section 17 for equipment costs. R100a, R100b, R-100c refer to the same vessel.

Batch API Process: Crystallization Vessel

Identification:	**Item**	*Crystallization Vessel*	Date:	21 April 2020
	Item No.	R-100c	By:	ACL
	No. Required	1		

Function: Carry out crystallization to precipitate API product from solution

Operation: Batch

Materials Handled	*7*	*8*	*9*	*10*
Temperature (°C)	80	20	20	12
Pressure (bar)	1	1	1	1
Mass (kg)	2029.22	145.06	1	2175.28
Component Mass (kg)				
THF	12.10	0	0	12.10
Ethanol	1816.79	145.06	0	1961.85
Starting Material	0.38	0	0	0.38
Product	199.95	0	0	200.95
Dry Seed	0	0	1	0
30% w/w Ethylene Glycol	0	0	0	0

Design Data:

Vessel Volume: 4000 L
Jacket Volume: 560 L
Heat Transfer Area: 7.02 m^2
Average Heat Transfer Coefficient: 159 W/m^2-K
Inner Diameter of Vessel: 1.8 m
Diameter Including Jacket: 1.9 m
Jacket inlet nozzle diameter: 52.5mm
Agitator Length: 0.750 m
Agitator Speed: 50
Material of Construction: Glass Lined Stainless Steel
Thickness of Lining: 1.5 mm
Thermal Conductivity of Lining: 1 W/m-K
Thickness of Wall (Stainless Steel): 20 mm
Thermal Conductivity of Wall: 40 W/m-K
Vessel Pressure: 1 bar
Company and Name: De Dietrich AE 4000

Utilities per Batch: See section 14.2 for additional detail

Comments and Drawings: See PFD in Figure 12.1. Jacket material ignored – Refer to Table 12.2.4. Refer to Section 25.2 for detailed specifications and Section 17 for equipment costs. R100a, R100b, R-100c refer to the same vessel.

Batch API Process: Filter Dryer

Identification:	**Item**	*Filter Dryer*	Date:	21 April 2020
	Item No.	FD-100	By:	ACL
	No. Required	1		

Function: Filter product from mother liquor and dry final API product

Operation: Batch

Materials Handled	*10*	*11*	*12*
Temperature (°C)	12	12	12
Pressure (bar)	1	1	1
Mass (kg)	2175.28	19991.42	183.86
Component Mass (kg)			
THF	12.10	12.10	0
Ethanol	1961.85	1961.85	0
Starting Material	0.38	0.38	0
Product	200.95	17.09	183.86
Dry Seed	0	0	0
30% w/w Ethylene Glycol	0	0	0

Design Data:
Vessel Volume: 4660 L
Wet Cake Volume: 1,600 L
Filtration Surface: 4.08 m^2
Material of Construction: C-22 Hastelloy
Pressure Range: -1 to 3 bar
Max Temperature: 130 °C
Company and Name: De Dietrich Nutsche Filter Dryer

Utilities per Batch: 502.5 kWh

Comments and Drawings: See PFD in Figure 12.1. Refer to Section 25.4 for detailed specifications and Section 17 for equipment costs.

Batch API Process: Steam Jacket Heat Exchanger

Identification:	**Item**	*Steam Jacket HX*	Date:	21 April 2020
	Item No.	E-100	By:	ACL
	No. Required	1		

Function: Heat jacket fluid with to maintain temperature in the vessel

Operation: Continuous

Materials Handled
Shell Side: Steam
Tube Side: 30 % w/w Ethylene Glycol

Design Data:
Max Heat Duty: 1.15×10^6 kJ/hr
Min Heat Duty: 2.94×10^5 kJ/hr
Material of Construction: Stainless Steel
Heat Transfer Coefficient: 750 W/m^2-K
Surface Area: 6 m^2
Type: Fixed Head
Tube Length: 2.4 m

Utilities per Batch: 2957 kg of lps steam

Comments and Drawings: See PFD in Figure 12.1 and Tables 14.1.1, 14.1.2, and 14.1.3. Refer to section 25.2 for detailed design calculations and Section 17 for equipment costs.

Batch API Process: Water Jacket Heat Exchanger

Identification:	**Item**	*Water Jacket HX*	Date:	21 April 2020
	Item No.	E-101	By:	ACL
	No. Required	1		

Function: Heat or Cool jacket fluid to maintain temperature in the vessel

Operation: Continuous

Materials Handled
Shell Side: Hot or Chilled Water
Tube Side: 30% w/w Ethylene Glycol

Design Data:
Max Heat Duty (Heating): 9.95×10^4 kJ/hr
Min Heat Duty (Heating): 4.31×10^3 kJ/hr
Max Heat Duty (Cooling): -1.13×10^5 kJ/hr
Min Heat Duty (Cooling): -1.40×10^4 kJ/hr
Heat Transfer Coefficient: 500 W/m^2-K
Surface Area: 10 m^2
Type: Fixed Head
Tube Length: 2.4m

Utilities per Batch: 4,402 m^3 of hot water and 5,317 GJ of chilled water

Comments and Drawings: See PFD in Figure 12.1 and Tables 14.1.1, 14.1.2, and 14.1.3. Refer to Section 25.2 for detailed design calculations and Section 17 for equipment costs.

Batch API Process: Distillate Condenser (Heat Exchanger)

Identification:	**Item**	*Distillate Condenser*	Date:	21 April 2020
	Item No.	E-102	By:	ACL
	No. Required	1		

Function: Condense distillate leaving the vessel

Operation: Continuous

Materials Handled	Hot In (5)	Hot Out (6)	Cold In
Temperature (°C)	80	80	20
Pressure (bar)	1	1	1
Mass (kg)	7126.41	7126.41	
Mass Flow (kg/hr)			6500 kg/hr
Component Mass (kg)			
THF	2030.19	2030.19	0
Ethanol	5096.22	5096.22	0
Starting Material	0	0	0
Product	0	0	0
Dry Seed	0	0	0
30% w/w Ethylene Glycol	0	0	0

Design Data:
Max Heat Exchanged:
404,009 kJ/hr
Material of Construction: Stainless Steel
Heat Transfer Coefficient: 500 W/m^2-K
Surface Area: 6 m^2
Type: Fixed Head
Tube Length: 2.4 m
Max LMTD: 52.4

Utilities per Batch: 8484 m^3 of cooling water

Comments and Drawings: See PFD in Figure 12.1. Refer to section 25.2 for detailed design calculations and Section 17 for equipment costs.

Batch API Process: THF Pump

Identification:	**Item**	*THF Pump*	Date:	21 April 2020
	Item No.	P-100	By:	ACL
	No. Required	1		

Function: Transfer solvent from storage tanks to reaction vessel

Operation: Continuous

Materials Handled	Feed	Discharge (1)
Temperature (°C)	20	20
Pressure (bar)	1	1
Mass (kg)	2042.29	2042.29
Component Mass (kg)		
THF	2042.29	2042.29
Ethanol	0	0
Starting Material	0	0
Product	0	0
Dry Seed	0	0
30% w/w Ethylene Glycol	0	0

Design Data:
Type of Pump: Centrifugal
Pressure Change: 3 bar
Material of Construction: Stainless Steel
Head: 35 m
Volumetric Flow Rate: 20 L/s
Pump Efficiency: 0.67
Shaft rpm: 1,800
Net Work: 14.08 hp

Utilities per Batch: 0.300 kWh

Comments and Drawings: See PFD in Figure 12.1. Pressure drop only occurs due to frictional losses in pipes. 3 bar drop assumed to accommodate all processes. See Section 25.2 for design calculations and Section 17 for equipment costs.

Batch API Process: Starting Material Powder Pump

Identification:	**Item**	*SM Powder Pump*	Date:	21 April 2020
	Item No.	P-101	By:	ACL
	No. Required	1		

Function: Automate transfer of hazardous staring material from T-101 to R-100a

Operation: Continuous

Materials Handled	Feed	Discharge (2)
Temperature (°C)	20	20
Pressure (bar)	1	1
Mass (kg)	200.33	200.33
Component Mass (kg)		
THF	0	0
Ethanol	0	0
Starting Material	200.33	200.33
Product	0	0
Dry Seed	0	0
30% w/w Ethylene Glycol	0	0

Design Data:
Type of Pump: Pneumatic
Pressure Change: 3 bar
Material of Construction: Hastelloy
Head: 15.24 m
Volumetric Flow Rate: 0.10 L/s
Outlet Flange Diameter: 0.10 m
Shaft rpm: 1,800
Net Work: 5 hp

Utilities per Batch: 2.07 kWh

Comments and Drawings: See PFD in Figure 12.1. Refer to Section 25.2 for detailed specifications and Section 17 for equipment costs.

Batch API Process: Jacket Fluid Pump				
Identification:	**Item**	*Jacket Fluid Pump*	Date:	21 April 2020
	Item No.	P-102	By:	ACL
	No. Required	1		
Function: Pump around external jacket fluid to maintain temperature in vessel				
Operation: Continuous				
Materials Handled 30% w/w Ethylene Glycol at Different Flow rates and temperatures. See Tables 12.2.2, 12,2.3, and 12.2.4 for more information.				
Design Data:	Type of Pump: Centrifugal Pressure Change: 3 bar Material of Construction: Stainless Steel Head: 28.11 m Volumetric Flow Rate: 4 L/s Pump Efficiency: 0.47 Shaft rpm: 1,800 Net Work: 4.11 hp			
Utilities per Batch: 132.17 kWh				
Comments and Drawings: See PFD in Figure 12.1 Pressure drop only occurs due to frictional losses in pipes. 3 bar drop assumed to accommodate all processes. See Section 25.2 for design calculations and Section 17 for equipment costs.				

Batch API Process: Distillate Pump

Identification:	**Item**	*Distillate Pump*	Date:	21 April 2020
	Item No.	P-103	By:	ACL
	No. Required	1		

Function: Move Condensed Distillate to Waste Tank

Operation: Continuous

Materials Handled	Feed	Discharge (6)
Temperature (°C)	20~30	68.5~80
Pressure (bar)	1	1
Mass (kg)	6574.12	6574.12
Component Mass (kg)		
THF	2031.3	2031.3
Ethanol	4542.82	4542.82
Starting Material	0	0
Product	0	0
Dry Seed	0	0
30% Ethylene Glycol	0	0

Design Data:
Type of Pump: Centrifugal
Pressure Change: 3 bar
Material of Construction: Stainless Steel
Head: 38.1 m
Volumetric Flow Rate: 10 L/s
Pump Efficiency: 0.59
Shaft rpm: 1,800
Net Work: 8.05 hp

Utilities per Batch: 1.20 kWh

Comments and Drawings: See PFD in Figure 12.1. Pressure drop only occurs due to frictional losses in pipes. 3 bar drop assumed to accommodate all processes. See Section 25.2 for design calculations and Section 17 for equipment costs.

Batch API Process: Ethanol Pump

Identification:	**Item**	*Ethanol Pump*	Date:	21 April 2020
	Item No.	P-104	By:	ACL
	No. Required	1		

Function: Move ethanol from storage tank to vessel for solvent swap

Operation: Continuous

Materials Handled	Feed	Discharge (4)
Temperature (°C)	20	20
Pressure (bar)	1	1
Mass (kg)	6913.01	6913.01
Component Mass (kg)		
THF	0	0
Ethanol	6913.01	6913.01
Starting Material	0	0
Product	0	0
Dry Seed	0	0
30 % Ethylene Glycol	0	0

Design Data:
Type of Pump: Centrifugal
Pressure Change: 3 bar
Material of Construction: Stainless Steel
Head: 39 m
Volumetric Flow Rate: 3.15 L/s
Pump Efficiency: 0.44
Shaft rpm: 1,800
Net Work: 3.49 hp

Utilities per Batch: 1.58 kWh

Comments and Drawings: See PFD in Figure 12.1. Pressure drop only occurs due to frictional losses in pipes. 3 bar drop assumed to accommodate all processes. See Section 25.2 for design calculations and Section 17 for equipment costs.

Batch API Process: Mother Liquor Pump

Identification:	**Item**	*Mother Liquor Pump*	Date:	21 April 2020
	Item No.	P-105	By:	ACL
	No. Required	1		

Function: Move mother liquor into waste tank for disposal

Operation: Continuous

Materials Handled	Feed (11)	Discharge
Temperature (°C)	12	12
Pressure (bar)	1	1
Mass (kg)	1991.42	1991.42
Component Mass (kg)		
THF	12.10	12.10
Ethanol	1961.85	1961.85
Starting Material	0.38	0.38
Product	17.09	17.09
Dry Seed	0	0
30% w/w Ethylene Glycol	0	0

Design Data:
Type of Pump: Centrifugal
Pressure Change: 3 bar
Material of Construction: Stainless Steel
Head: 38.78 m
Volumetric Flow Rate: 12.6 L/s
Pump Efficiency: 0.62
Shaft rpm: 1,800
Net Work: 9.66 hp

Utilities per Batch: 0.332 kWh

Comments and Drawings: See PFD in Figure 12.1. Pressure drop only occurs due to frictional losses in pipes. 3 bar drop assumed to accommodate all processes. See Section 25.2 for design calculations and Section 17 for equipment costs.

Batch API Process: API Product Powder Pump

Identification:	**Item**	*API Powder Pump*	Date:	21 April 2020
	Item No.	P-106	By:	ACL
	No. Required	1		

Function: Automate transfer of hazardous staring material from T-101 to R-100a

Operation: Continuous

Materials Handled	Feed	Discharge (2)
Temperature (°C)	20	20
Pressure (bar)	1	1
Mass (kg)	183.86	183.86
Component Mass (kg)		
THF	0	0
Ethanol	0	0
Starting Material	0	0
Product	183.86	183.86
Dry Seed	0	0
30% w/w Ethylene Glycol	0	0

Design Data:
Type of Pump: Pneumatic
Pressure Change: 3 bar
Material of Construction: Hastelloy
Head: 15.24 m
Volumetric Flow Rate: 0.10 L/s
Outlet Flange Diameter: 0.10 m
Shaft rpm: 1,800
Net Work: 5 hp

Utilities per Batch: 1.94 kWh

Comments and Drawings: See PFD in Figure 12.1. Refer to Section 25.2 for detailed specifications and Section 17 for equipment costs.

Batch API Process: THF Horizontal Pressure Vessel

Identification:	**Item**	*THF Storage Tank*	Date:	21 April 2020
	Item No.	T-100	By:	ACL
	No. Required	1		

Function: Store THF solvent used in process

Operation: Storage

Materials Handled:	To process (1)
Temperature (°C)	20
Pressure (bar)	1
Mass (kg)	2042.29
Component Mass (kg)	
THF	2042.29
Ethanol	0
Starting Material	0
Product	0
Dry Seed	0
30% w/w Ethylene Glycol	0

Design Data:
Time Stored: 1 week
Material of Construction: Stainless Steel 304
Diameter: 1.83 m
Length of Tank: 5.49 m
Tank Volume: 15142 l
Pressure: 1 bar
Temperature: 20 °C
Wind/earthquake protection

Comments and Drawings: See PFD in Figure 12.1. Refer to section 25.2 for detailed design calculations and Section 17 for equipment costs.

Batch API Process: Ethanol Horizontal Pressure Vessel

Identification:	**Item**	*Ethanol Storage Tank*	Date:	21 April 2020
	Item No.	T-101	By:	ACL
	No. Required	1		

Function: Store ethanol solvent used in process

Operation: Storage

Materials Handled:	To process (4)
Temperature (°C)	20
Pressure (bar)	1
Mass (kg)	7058.1
Component Mass (kg)	
THF	0
Ethanol	7058.1
Starting Material	0
Product	0
Dry Seed	0
30% w/w Ethylene Glycol	0

Design Data:
Time Stored: 1 week
Material of Construction: Stainless Steel 304
Diameter: 2.74 m
Length of Tank: 7.32 m
Tank Volume: 45425 l
Pressure: 1 bar
Temperature: 20 °C
Wind/earthquake protection

Comments and Drawings: See PFD in Figure 12.1. Refer to section 25.2 for detailed design calculations and Section 17 for equipment costs.

Batch API Process: Distillate Waste Horizontal Pressure Vessel

Identification:	**Item**	*Distillate Waste Tank*	Date:	21 April 2020
	Item No.	W-100	By:	ACL
	No. Required	1		

Function: Store distillate waste generated from process

Operation: Storage

Materials Handled:	From process (6)
Temperature (°C)	20
Pressure (bar)	1
Mass (kg)	7126.41
Component Mass (kg)	
THF	2030.19
Ethanol	5096.22
Starting Material	0
Product	0
Dry Seed	0
30 % Ethylene Glycol	0

Design Data:
Time Stored: 1 week
Material of Construction: Stainless Steel
Diameter: 2.74 m
Length of Tank: 7.32 m
Tank Volume: 45425 l
Pressure: 1 bar
Temperature: 20 °C
Wind/earthquake protection

Comments and Drawings: See PFD in Figure 12.1. Refer to section 25.2 for detailed design calculations and Section 17 for equipment costs.

Batch API Process: Mother Liquor Waste Horizontal Pressure Vessel

Identification:	**Item**	*ML Waste Tank*	Date: 21 April 2020
	Item No.	W-101	By: ACL
	No. Required	1	

Function: Store mother liquor waste generated from crystallization

Operation: Storage

Materials Handled:	From process (11)
Temperature (°C)	12
Pressure (bar)	1
Mass (kg)	1991.42
Component Mass (kg)	
THF	12.10
Ethanol	1961.85
Starting Material	0.38
Product	17.09
Dry Seed	0
30% w/w Ethylene Glycol	0

Design Data:
Time Stored: 1 week
Material of Construction: Stainless Steel 304
Diameter: 1.83 m
Height or Tank: 5.49 m
Tank Volume: 15142 l
Pressure: 1 bar
Temperature: 20 °C

Comments and Drawings: See PFD in Figure 12.1. Refer to section 25.2 for detailed design calculations and Section 17 for equipment costs.

Section 17: Equipment Cost Summary

17.1 Equipment Cost Summary

Table 17.1.1 Summary of Equipment Costs for Halfaxia Batch Process

Unit ID	**Type**	**Purchase Cost ($)**	**Bare Module Factor**	**Bare Module Cost ($)**	**Unit Type**
R-100a-c	Fabricated Equipment	220,000	4.05	891,000	Vessel
FD-100	Fabricated Equipment	800,000	4.05	3,240,000	Filter Dryer
E-100	Fabricated Equipment	52,377	3.17	166,035	Heat Exchanger
E-101	Fabricated Equipment	52,377	3.17	166,035	Heat Exchanger
E-102	Fabricated Equipment	52,377	3.17	166,035	Condenser
P-100	Process Machinery	17,535	3.30	57,866	Pump
P-101	Process Machinery	35,000	3.30	155,500	Pump
P-102	Process Machinery	14,467	3.30	47,741	Pump
P-103	Process Machinery	14,486	3.30	47,804	Pump
P-104	Process Machinery	14,346	3.30	47,342	Pump
P-105	Process Machinery	15,911	3.30	52,506	Pump
P-106	Process Machinery	35,000	3.30	155,500	Pump
T-100	Storage	66,314	3.05	202,258	Pressure Vessel
T-101	Storage	105,805	3.05	322,704	Pressure Vessel
W-100	Storage	105,805	3.05	322,704	Pressure Vessel
W-101	Storage	66,314	3.05	202,258	Pressure Vessel
Total Bare Module Cost: $6,243,288					

Table 17.1.1 displays the equipment costs required for the pharmaceutical batch process. All of the equipment costs except for R-100a-c and FD-100 were calculated using equations provided in *Product and Process Design Principles* and the spreadsheet provided by the professors of CBE 459 [11]. A CE cost index of 600 was used to account for the inflation in 2020. Appropriate bare module costs were applied to the pumps, heat exchangers, condensers, and storage tanks following guidelines from Seider et al. Detailed calculations for pump, storage tanks, and heat exchanger sizing are described in section 25.2 of the appendix.

17.2 Vessel and Filter Dryer

The purchase costs for the 4000 L glass lined vessel (R-100a-c) and filter dryer (FD-100) were acquired using direct quotes from the manufacturer, De Dietrich. These pieces of equipment have purchase costs of $220,000 and $800,000 for the vessel and filter dryer, respectively (See Appendix 25.4). The bare module costs for R-100a-c and FD-100 were assumed to be 4.05, which follows the breakdown presented in Table 17.2.1. Any bare module factor that is close to the factors for storage vessels in Seider et al. was deemed appropriate for R-100a-c and FD-100. The total bare module costs for the vessel and filter dryer are $891,000 and $3,240,000, respectively.

Table 17.2.1 Derived Bare Module Factor Considerations

Cost Type	Percentage of Equipment Purchase Cost (%)
Installation Materials	70
Installation labor	70
Freight, Insurance, and Taxes	15
Construction Overhead	70
Contractor Engineering Expenses	80
Total Bare Module Cost	4.05

17.3 Pumps

Using equations in Chapter 16 of Seider et al., the total bare module cost for all 4 centrifugal pumps used in the process is $253,259. This cost also includes the price for 1,800 shaft rpm electric motors with a type factor of 1.5. The cost depends on the liquid flow rate, pressure drop, and density of the fluid flowing through the pump. Due to the nature of this batch process, pumps are required to overcome frictional forces to move fluid from one area to another. Therefore, an approximate pressure drop of 3 bar and head of 30 m were used as baselines to estimate the flow rate throughout the pump. Stainless steel pumps were designed to account for cleanliness and corrosion resistance, allowing for a material factor of 2. Using quotations from the manufacturer in Section 25.4, the specialty powder pumps P-101 and P-106 each have a purchase cost of $35,000. The bare module cost for all pumps and electric motors is 3.30, following guidelines from *Product and Process Design Principles*.

17.4 Heat Exchangers and Condensers

The equations provided in Chapter 16 of Seider et al. require a minimum heat transfer area of 14 square meters to calculate the costs of shell and tube heat exchangers. The areas of E-100, E-101, and E-102 fall under the minimum required area at 6, 10, and 6 square meters respectively. However, the costs equations were still utilized by assuming all three pieces of equipment had a heat transfer area of 14 square meters. The difference in cost between the actual heat exchanger sizing and the assumed will be negligible in the overall economic analysis for this process. All heat exchangers have a tube length of 2.4 m and assume a fixed head configuration. Following pharmaceutical standards, the shell and tube portions of each equipment are constructed with stainless steel. This creates a material factor of 3.78 and a length factor of 1.25. The bare module factor is 3.17 following guidelines from *Product and Process Design Principles*.

17.5 Storage and Waste Tanks

The four storage and waste tanks are horizontal pressure vessels operating at atmospheric pressure. Their volumes were determined using a guideline from *Product and Process Design Principles* to size pressure vessels 1.5 times the size of the transport vehicle. Bulldog Steel Products, Inc., provides standard dimensions (diameter and length) associated with vessel capacity [12]. These dimensions were used to calculate the bare-module cost, using a Materials-of-Construction Factor F_m of 1.7 for Stainless Steel 304. Table 16.11 from *Product and Process Design Principles* gives a bare-module factor of 3.05 for horizontal pressure vessels. The total bare-module cost for the four horizontal pressure vessels is $1,049,924 and the total purchase cost is $344,238.

17.6 Equipment Cost Comparison

The pie chart below shows a breakdown of all of the costs involved in this process. Specialty equipment, such as the De Dietrich vessel and filter dryer, compose the majority of the equipment costs at 67%. These pieces of equipment are commonly used in the pharmaceutical industry and therefore come highly recommended by J&J. The 4000 L vessel comes equipped with all necessary components including a jacket, agitators, and spray nozzles for cleaning. Additionally, the storage and waste tanks contribute to a large portion of the cost at 17%. Having sufficient waste and storage tanks ensures enough inventory is available to create several batches. Heat exchangers and pumps represent the minority of costs in the overall manufacturing process.

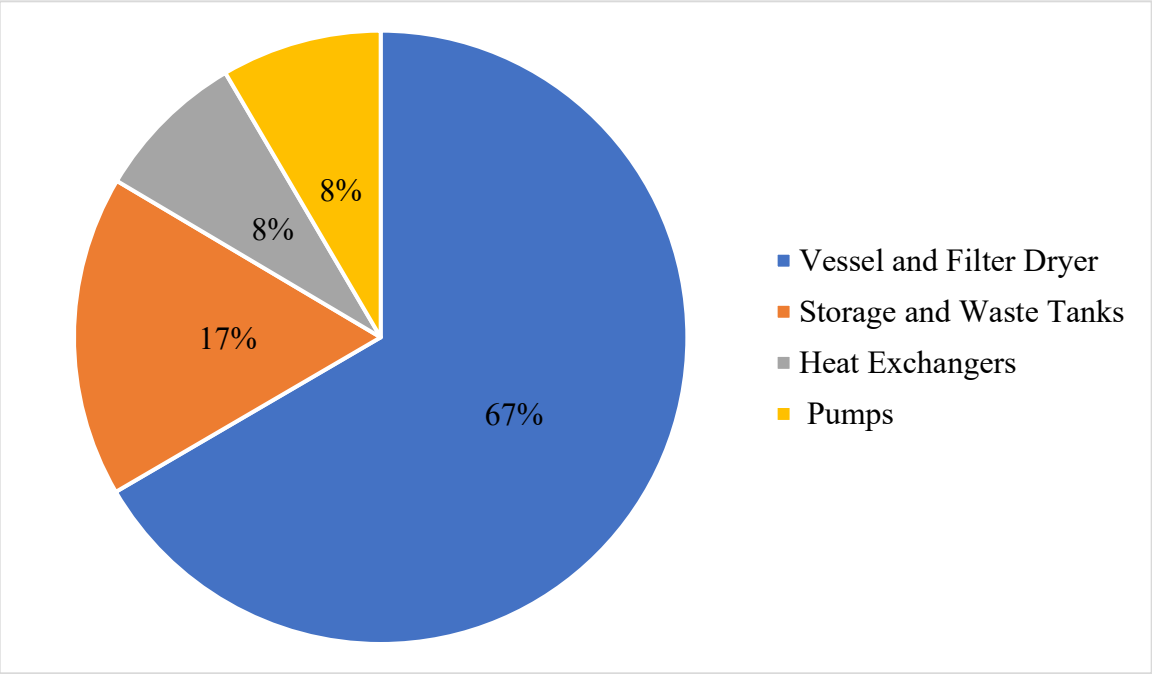


Figure 17.6.1 Equipment Cost Breakdown for Halfaxia Synthesis

Section 18: Fixed Capital Investment Summary

18.1 Total Capital Investment

The CBE 459 spreadsheet is used for Sections 18, 19, and 21 of the report. The total capital investment for the process is the sum of the total permanent investment and the total working capital, as shown in the equation below. The TCI for this process is $31,940,569 with $7,232,630 for the TPI and $24,707,939 for the WC.

$$C_{TCI} = C_{TPI} + C_{WC} \qquad \text{(Equation 18.1.1)}$$

The working capital costs include costs for inventory, accounts receivable, cash reserves, and accounts payable. The total permanent investment includes the bare module costs, direct permanent investment, total depreciable capital, and cost of land, royalties and startup. This manufacturing process will be built in Mumbai, India due to cheaper costs of labor and the presence of existing J&J pharmaceutical plants.

18.2 Working Capital

Working capital refers to the funds required by J&J to meet their obligations until payments are received for the API produced. Following accountant standards, working capital is typically provided for a one-month period of plant operation. Therefore 30 days of cash reserves are provided for utilities, operations, maintenance, operating overhead, property taxes, insurance, and depreciation. The cash reserves did not include raw materials and amounted to 8.33% of the annual cost of manufacture. Additionally, 30 days are provided for accounts receivable and accounts payable. The inventory of the product, Halfaxia, is set for 4 days and the inventory for raw materials is set for 2 days. Assuming that the manufacturing process would be co-located with the drug product site, 4 days of inventory is considered reasonable for the API product. Although 2 days of raw material is suitable inventory for the starting material, it was considered too low for the solvents used in the process. The spreadsheet used cannot specify different days of inventory

depending on the raw material, therefore the value remains at 2 days. This assumption is validated by the fact that the starting material has the highest cost in the raw material inventory. A summary of the working capital costs is displayed in Table 18.2.1. Note that the total working capital is the undiscounted version.

Table 18.2.1 Breakdown of Working Capital Costs Over the First Three Years of Production

	2021	2022	2023
Accounts Receivable ($)	21,071,356	10,535,678	10,535,678
Cash Reserves ($)	178,571	89,286	89,286
Accounts Payable ($)	(12,534,204)	(6,267,102)	(6,267,102)
Halfaxia Inventory ($)	2,809,514	1,404,757	1,404,757
Raw Materials ($)	828,732	414,366	414,366
Total	12,353,969	6,176,985	6,176,985
Present Value at 15%	10,742,582	4,670,688	4,061,468
Total Working Capital ($)		**$24,707,939**	

18.3 Total Permanent Investment

The total permanent investment for this project totals to $7,232,630 and is summarized by the results in Table 18.3.2. 100% of the total permanent investment occurs in the first year of construction in 2021. Although some companies do not have the capability to invest a large portion of money in a single year, typical pharmaceutical companies are well equipped to handle this investment in the first year. The total bare module costs for the equipment used in this process included the costs for fabricated equipment, process machinery, storage, and other equipment. Section 17 provides more details into how these costs were sourced or calculated. For the direct

permanent investment, the costs of site preparations and land are set to 0% of the total bare module costs and total depreciable capital. This API batch manufacturing process occurs on an existing plant, which allows for these costs to be negligible. Other assumptions for determining the total permanent investment followed standard guidelines in Seider et al., 2017 and include the cost of contingencies and contractor fees, service facilities, and plant start up. The cost of royalties and utility plants are negligible. Table 18.3.1 outlines these assumptions used to determine the total permanent investment

Table 18.3.1 Assumptions Leading to the Total Permanent Investment for 100% of TPI in First Year of Construction

Cost for TPI	Assumption
Site Preparations	0% of Total Bare Module Costs
Service Facilities	5% of Total Bare Module Costs
Contingencies and Contractor Fees	18% of Direct Permanent Investment
Land	0% of Total Depreciable Capital
Plant Start Up	10% of Total Depreciable Capital

Table 18.3.2 Calculation of the Total Permanent Investment

Total Bare Module Costs	
Fabricated Equipment	$4,629,105
Process Machinery	$564,259
Spares	-
Storage	$1,049,924
Other Equipment	-
Catalysts	-
Computers, Software, Etc.	-
Total Bare Module Costs	**$6,243,288**
Direct Permanent Investment	
Cost of Site Preparations	-
Cost of Service Facilities	$312,164
Allocated Costs for Utility Plants	-
Direct Permanent Investment	**$6,555,452**
Total Depreciable Capital	
Cost of Contingencies & Contractor Fees	$1,179,981
Total Depreciable Capital	**$7,735,434**
Total Permanent Investment	
Cost of Land	-
Cost of Royalties	-
Cost of Plant Start-Up	$773,543
TPI Unadjusted	$8,508,977
Site Factor	0.85
Total Permanent Investment	**$7,232,630**

Therefore, the total capital investment following equation 18.1.1 is $31,940,569.

Section 19: Operating Cost and Cost of Manufacture

19.1 General Operations

This pharmaceutical API batch process occurs in India with a start year of 2020. It will take 1 year to design the facility, 1 year to construct the facility, and 10 years for production.

API patents usually hold for 10 years, during which the company has a period of time to sell the product for the most competitive price. After the patent expires, other companies start to produce the same product which lowers the selling price [13]. Therefore, this economic analysis was only conducted for the 10 years patent holding period where J&J can use the competitive selling price of 30$/gram of Halfaxia. Analyzing varying economics due to selling price is beyond the scope of this project.

The batch production process will adopt a discrete 24 hours a day and 7 day per week operation. Including the time for filtering and drying, each batch takes 76.8 hours to complete, which indicates the need for the facility to operate 24/7 to avoid mid-batch interruptions. The facility will run for 330 days or 11 months out of the year, with an operating factor 0.9041. Because the fixed costs used in this economic analysis apply to each year, having almost a full year operation allows for the maximum use of these costs. The extra month where the plant is not operating helps account for vacation days and cleanup processes between batches. As described in detail in Section 20 of the report, this pharmaceutical batch process must work for different types of products. Proper extensive cleaning must be implemented between batches of different types to avoid contamination. However, it is important to note that for in-between batches of the same type, such as Halfaxia, cleaning can occur during the drying time of the product, as described in Section 20.

19.2 Variable Costs – Raw Materials, Utility, By Products, and General Expenses

The raw materials in this process include ethanol, THF, starting material, and 30% w/w ethylene glycol. The starting material price was provided by the project author at a value of 10$/gram. The prices for the other raw materials were acquired from sources online described in Section 11. Table 19.2.1 summarizes the required ratio of raw materials to grams of API produced and the associated costs.

Table 19.2.1 Raw Material Requirements and Costs for API Manufacturing Process

Raw Material	Required Ratio (gram/gram of Halfaxia)	Cost of Raw Material ($/gram)
Ethanol	38.38	0.0049
THF	11.11	0.12
Starting Material	1.09	10.00
30% w/w Ethylene Glycol	3656.00	0.0014
Dry Seed	0.0054	30.00
Total Weighted Average	**$17.70 per gram of Halfaxia**	

The utilities required for this process include chilled water, hot water, low pressure steam and electricity to power the pumps, agitators, and filter dryer. The total utility requirements are listed in Table 19.2.2.

Table 19.2.2 Utility Requirements and Costs for API Manufacturing Process

Utility	Unit	Required Ratio (per gram of Halfaxia)	Cost of Utility ($/unit)
Low Pressure Steam	kg	0.016	0.00132
Chilled Water	GJ	0.0289	5.00
Hot or Cooling Water	m^3	0.070	0.027
Electricity	kWh	0.0038	0.070
Total Weighted Average		**$0.147 per gram of Halfaxia**	

Other than the API product, there are currently no by-products that can be sold for profit in this manufacturing process. Opportunities to sell the THF and ethanol distillate were explored, as some companies will use more rigorous distillation efforts to separate and sell the two components. However, the profit received from selling the distillate would be minimal when compared to the money gained from the actual API product. Additionally, the costs to dispose of waste product would most likely offset the profits gained from selling the distillate. Therefore, this profit avenue was neglected.

General expenses include the costs of selling and transfer, direct research, allocated research, administrative expenses, and management incentive compensation. Following guidelines from Chapter 17 of Seider et al., the selling expenses cover the costs involved for the sales office, shipping, and sales representatives. However, the API produced is not in the final sellable form and will simply be transferred to a co-located drug product site for further processing. Therefore, the selling and transfer expenses were assumed as 0% of the total sales. Similarly, due to confidentiality, this process does not include the extensive costs for research and development and clinical trials. However, some research costs must be accounted for to optimize the cleaning, maintenance, and performance of the manufacturing process over time. The research costs were slightly reduced from the recommended percentages, and the results the general expenses are displayed in Table 19.2.3.

Table 19.2.3 Summary of Assumptions for General Expenses

General Expense	Percentage of Sales
Selling/Transfer Expenses	0.00%
Direct Research	2.00%
Allocated Research	0.50%
Administrative Expense	2.00%
Management Incentive Compensation	1.25%

As shown in Table 19.2.4, combining the costs of raw materials, utilities, and general expenses creates annual variable costs of $371,645,900.

Table 19.2.4 Summary of Variable Costs for Annual Halfaxia Production

General Expenses	
Selling/Transfer Expenses	-
Direct Research	$11,,394,141
Allocated Research	$2,848,535
Administrative Expenses	$11,394,141
Management Incentive Compensation	$7,121,338
Total General Expenses	$32,758,155
Raw Materials	$336,096,804
Utilities	$2,790,941
Total Variable Costs	**$371,645,900**

19.3 Fixed Costs – Operations, Maintenance, and Overhead

The wage rate was adjusted to $9/hr to account for the cost of living in India. This pay rate is based on an average pharmaceutical process engineer salary of $8.40 for a typical work week in India [14]. Because this plant requires minimal exposure between the operators and the process, only 2 operators were deemed necessary for each of the 5 shifts. Additionally, only 1 engineer and 1 person in the laboratory were required. Table 19.3.1 summarizes additional assumptions used to calculate the operations fixed costs.

Table 19.3.1 Breakdown of Assumptions used to Calculate Fixed Operating Costs

Operations	Details
Operators per Shift	2 (assuming 5 shifts)
Direct Wages and Benefits	$9/operator hour
Direct Salaries and Benefits	15% of Direct Wages and Benefits
Operating Supplies and Services	6% of Direct Wages and Benefits
Ethnical Assistance to Manufacturing	$20,000 per year, per operator
Control Laboratory	$50,000 per year, per operator

The fixed maintenance and operating overheard costs mainly followed recommendations from Chapter 17 of Seider et al. For maintenance costs, the general plant overheard was increased from 5.00% to 7.00% of maintenance wages and benefits to account for the costs of cleaning in between batches. Increasing the maintenance percentage helps account for the unknown cleaning steps that occur between batches of different types. Tables 19.3.2 and 19.3.3 provide details on the assumptions used to find the remaining fixed costs.

Table 19.3.2 Breakdown of Assumptions used to Calculate Fixed Maintenance Costs

Operations	Details
Wages and Benefits	4.5% of Total Depreciable Capital
Salaries and Benefits	25% of Maintenance Wages and Benefits
Materials and Services	100% of Maintenance Wages and Benefits
Maintenance Overhead	7% of Maintenance Wages and Benefits

Table 19.3.3 Breakdown of Assumptions used to Calculate Fixed Operating Overhead Costs

Operations	Details
General Plant Overhead	7.10% of Maintenance and Operations Wages and Benefits
Mechanical Department Services	2.40% of Maintenance and Operations Wages and Benefits
Employee Relations Department	5.90% of Maintenance and Operations Wages and Benefits
Business Services	7.40% of Maintenance and Operations Wages and Benefits

Table 19.2.4 Summary of Fixed Costs for Annual Halfaxia Production

Operations	
Direct Wages and Benefits	$187,200
Direct Salaries and Benefits	$28,080
Operating Supplies and Services	$11,232
Technical Assistance to Manufacturing	$200,000
Control Laboratory	$500,000
Total Operations	**$926,512**
Maintenance	
Wages and Benefits	$348,095
Salaries and Benefits	$87,024
Materials and Services	$348,095
Maintenance Overhead	24,367
Total Maintenance	**$807,579**
Operating Overhead	
General Plant Overhead	$46,178
Mechanical Department Services	$15,610
Employee Relations Department	$38,373
Business Services	$48,129
Total Operating Overhead	**$148,291**
Property Taxes and Insurance	
Property Taxes and Insurance	$154,709
Total Fixed Costs	**$2,037,091**

Section 20: Other Important Considerations

20.1 Facility Design

The reaction vessel (R-100) will be placed on the first floor of the facility while the filter dryer (FD-100) will be placed on the ground floor. This will allow gravity to direct the flow of the slurry following the crystallization step from the reaction vessel into the filter dryer and eliminate any need for pumping or operator handling. The THF pressure vessel (T-100), ethanol pressure vessel (T-101), and distillate waste tank (W-100), along with their associated pumps, will be placed side-by-side on the first floor next to the reaction vessel. The jacket shell-and-tube heat exchangers and the distillate condenser will also be placed next to the reaction vessel. Floor space on the first floor should be allotted for storage of the 55-gallon drums containing starting material and the cheaper starting material. The mother liquor waste tank (W-101) and its pump will be placed on the ground floor next to the filter dryer. There should also be space on the ground floor for 55-gallon drums for storing the API once the drying step is completed. The facility should be built as an extension to an existing Johnson & Johnson manufacturing site; thus, bathrooms and office space will not be required for this facility. Utilities for this facility include cooling water, chilled water, and electricity. Safety showers and eye-washing stations should be built on both floors of the facility. A loading dock where tanker trucks will load and unload the compounds required to run the process and the waste material generated from the process should also be built.

The facility should be built with extended floor space for future equipment installation for other batch API processes. Since a reaction vessel and a filter dryer are typical in batch processes, the equipment we have selected can support production of other APIs in the future. The equipment is built with sturdy and corrosion-resistant material such as glass or stainless steel. Future expansion of the facility in producing Halfaxia could entail installing a second reaction vessel and filter dryer in order to produce more API faster.

20.2 Safety Considerations

As mentioned in Section 20.1 and in the Problem Statement, the handling of APIs is hazardous to human health. A potent API is typically in the form of a powder, and if ingested, inhaled, or touched, it could cause serious health-related injuries to the operators. Therefore, the process equipment and the facility should be designed in accordance to good manufacturing practice (GMP) designed for handling APIs.

The equipment for our process must provide an isolated and contained environment for each step of the process. The reactor and the filter dryers are glass-lined to prevent corrosion of the walls from the chemicals and potential leaks. These pieces of equipment are outfitted with internal spray balls that can safely wash the interiors of the reactor and the filter dryer with ethanol during the cleaning procedure. Operation of the spray balls are automatic and occurs immediately following the use of the equipment; thus, operators should not need to manually clean the equipment and risk exposure to the API. Furthermore, any equipment purchased should be industrial-grade and be designed to handle pharmaceutics, following GMP guidelines.

The process incorporates two centrifugal pumps and two powder pumps to transfer the ethanol, THF, and starting material, respectively, into the reactor. The transfer from the drums and the pressure vessel to the pump are conducted using split butterfly valves. These valves consist of an active valve and a passive valve that are hermetically sealed. Rotating these valves allows the flow of fluid. In this manner, there is no risk of API or starting material exposure to the operator, and there is no contamination of hazardous material into the workspace [15]. The powder pump relies on dense phase flow in order to allow the flow of solids into the receiving vessels and is specifically designed to eliminate contamination or exposure of the powder by preventing leakage of the powder into the environment. The connection between the reaction vessel and the filter dryer

relies on gravity to allow the contents of the reaction vessel to flow through a pipe into the filter dryer. This pipe can also be outfitted with split butterfly valves at both ends to ensure that the contents do not leak at the joints. The pipe transferring dry seed into the reaction vessel to initiate crystallization also has split butterfly valves at both ends to prevent contact with the dry seed. The second powder pump is used at the end of the process to transfer the API in powder form from the tray at the bottom of the filter dryer into 55-gallon drums. From the beginning of the process to the end, operators will not be in contact with any starting material, chemicals, or API, since centrifugal pumps and powder pumps will transfer all material to the corresponding vessel. Thus, the API is manufactured in a closed and controlled environment. Further testing of the process once the facility is built should be performed in order to ensure that the equipment is indeed safe for operators to handle.

Operators should wear personal protective equipment (PPE) when in the workspace. The PPE required are head covers, safety glasses, face masks, gloves, arm covers, lab coats or gowns, and shoe covers. The PPE should be sterile and single use. They are designed to limit operator exposure to the API and minimize or eliminate contact with any chemical in the facility.

The facility should be designed with GMP guidelines in place. The guidelines are titled "Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients" and are found on www.fda.gov. This article includes, but is not limited to, guidelines for quality control and management, process equipment, and facility design. The objective of the GMP guidelines is to provide a safe environment for operators to handle potent and hazardous chemicals by limiting exposure to these chemicals, and also to prevent contamination of the product and reactants. When constructing this facility, these guidelines should be consulted frequently to ensure that all practices are being followed.

20.3 Waste Disposal and Environmental Considerations

The batch process generates distillate waste consisting of ethanol and THF in solution, and mother liquor consisting of ethanol, THF, starting material, and product. The addition of a flash separation system or a distillation column to separate the waste materials is costly and difficult to ensure complete purity of these materials after separation. In addition, the starting material and API are toxic and health hazards to humans exposed to large quantities so even if ethanol and THF are separated from the starting material and API, they carry a high risk of potential contamination from the starting material and API. Disposal of these chemicals in a landfill also carries a risk of contamination of the environment and the groundwater. Thus, instead of installing a distillation column or disposing at a landfill, it is financially and ethically beneficial to incinerate the waste materials at an external disposal company. The storage tanks carrying the mother liquor and the distillate waste will be brought to the incinerator once a week to be disposed. However, incineration does release harmful carbon dioxide and nitrous oxide into the air, though with proper equipment and constant monitoring, these emissions can be reduced.

20.4 Operation of Reaction Vessel and Filter Dryer

As Figure 12.3.2 shows, there is overlap between when the reaction vessel is running and when the filter dryer is running. Cleaning is incorporated into the process in between use of each vessel; Johnson & Johnson recommended 12 hours for cleaning each vessel. In order to maximize the amount of product generated, the process should be run at all hours of the day. The reaction vessel is in use for approximately 46.7 hours. Immediately following completion of crystallization, the reaction vessel should begin its 12-hour cleaning, which is when the filter dryer can begin the filtration step. The filter dryer will still be operating when the reaction vessel is finished cleaning, and thus a second batch can begin in the reaction vessel while the first batch is drying in the filter

dryer. The first batch will finish drying while the second batch is completing its distillation solvent swap. Thus, there will be approximately 22 hours when the filter dryer is not in use. Alternating the use of the reaction vessel and the filter dryer will enable the production of two batches of API in approximately 117 hours, if the facility is run 24 hours a day.

Section 21: Profitability Analysis

21.1 Guidelines for Profitability Analysis

As described in section 19, this process will run for 330 days with an operating factor of 0.9041. Beginning in 2020, the plant will take 1 year for design, 1 year for construction, and 10 years for production. Additionally, 100% of the TPI will occur during the first year of construction. As described in section 18, the total capital investment for this process is $31,940,569. Due to the plant location in India, the tax rate and depreciation schedule were adjusted appropriately. The tax rate is increased to 30% and the depreciation follows a 20-year schedule of 15% per year of the undepreciated capital. The labor cost savings by placing the plant in India outweigh the increase in tax and depreciation. The adjusted depreciation schedule is shown in Table 21.2.1.

Table 21.1.1 Adjusted 20 Year Depreciation Schedule for India

Year	Depreciation
1	15.00%
2	12.75%
3	10.84%
4	9.24%
5	7.85%
6	6.67%
7	5.67%
8	4.82%
9	4.10%
10	3.48%
11	2.96%
12	2.52%
13	2.14%
14	1.82%
15	1.55%
16	1.31%
17	1.12%
18	0.95%
19	0.81%
20	0.69%

As mentioned in Section 19, this economic analysis is only conducted for the 10 years patent holding period where J&J can use the competitive selling price of 30$/gram of Halfaxia. Additionally, using guidelines form *Product and Process Design Principles* an inflation rate of 2% is used throughout the analysis. Table 21.1.2 summarizes the profitability measures achieved by this economic analysis with a production rate of 2,398 grams of Halfaxia per day. The Halfaxia API synthesis process proves to be very profitable in the pharmaceutical industry with an ROI of 400.53% and IRR of 331.79%.

Table 21.1.2 Profitability Measures for Halfaxia Synthesis

Internal Rate of Return (IRR)	331.79%.
Net Present Value (NPV)	$488,895,200
ROI Analysis (Third Production Year)	400.53%
Annual Sales	533,450,886
Annual Costs	(350,113,744)
Depreciation	(578,610)
Income Tax	(54,827,560)
Net Earnings	127,930,972
Total Capital Investment	31,940,569
ROI	400.53%

21.2 Cash Flow Model

The cash flow model assumes the process achieves 50% of production capacity in the first year of production. Additionally, it will take 2 years to reach the full design capacity of 90%. The results of the summarized cash flow model are displayed in Table 21.2.1. The full cash flow model is in Section 25.6 of the Appendix. The cumulative net present value at 15%, or discounted cash flow shows that the process begins to break even after the first year of production, which is

highlighted on the table. Overall, the net present value (NPV) totals to $488,895,200, which is a strong indicator of profitability.

Table 21.2.1 Summary of Cash Flow For Halfaxia Synthesis

Year	Cash Flow ($)	Cumulative Net Present Value at 15% ($)
2020	-	-
2021	(19,586,600)	(17,031,800)
2022	55,134,400	24,657,700
2023	88,120,000	82,598,000
2024	128,587,600	156,118,400
2025	131,117,100	221,306,800
2026	133,702,900	279,110,200
2027	136,346,000	330,367,700
2028	139,046,600	375,822,300
2029	141,805,200	416,132,200
2030	144,622,300	451,880,600
2031	172,206,400	488,895,200

21.3 General Considerations

The Halfaxia API synthesis process proves to be very profitable in the pharmaceutical industry with an ROI of 400.53% and IRR of 331.79%. It is important to note that although the internal rate of return is significantly higher than the set goal of 20% in the project statement, this process does not include the costs of research and development, clinical trials, FDA approval, and drug delivery processing. These costs remain confidential and were not provided for the economic analysis. Additionally, the exact market for this product remains confidential which allows for the assumption that all product produced will be sold. In reality, the quantity of product sold may be

less than what is produced in this process. Regardless, the large profitability of this product suggests the product will be successful in the market even with additional costs.

21.4 Sensitivity Analysis – Production Rate of Halfaxia

The production rate of Halfaxia has the most significant impact on the profitability of this process. Therefore, any efforts to reduce the downtime in between batches would increase the amount of product produced and boost profitability. Currently, the process takes a total of 76.8 hours to complete following the cost breakdown in Table 12.3.1 with a production rate of 2,398 grams of Halfaxia per day. The processes that take up the majority of time include distillation, crystallization, and drying. Most notably, the economics have been conducted assuming that 24 hours of drying time are required, with 12 of those hours used for cleaning the vessel. Therefore, 12 additional hours remain where the vessel is not actively producing product and the operators are waiting for the drying time to complete. Figure 21.4.1 provides an analysis to how the net present value changes when those 12 hours of downtime are eliminated.

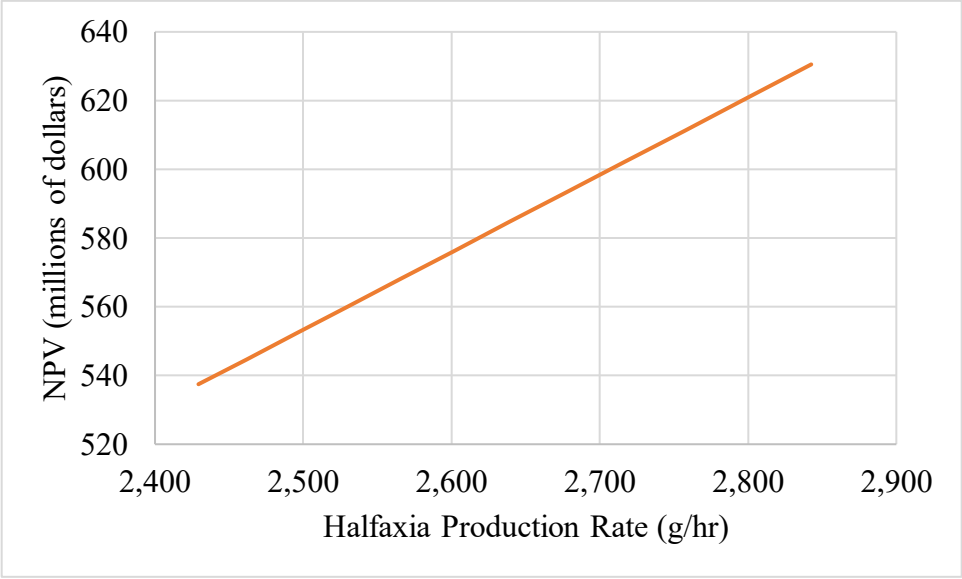


Figure 21.4.1 Plot of NPV vs. Halfaxia Production Rate. Eliminating all 12 hours of downtime causes the NPV to increase by 18.9%.

The x-axis represents the production rate of Halfaxia with each point corresponding to 1 less hour of down time. The production rate of 2842 g/hr corresponds to a process that would take 64.8 hours, which completely eliminates the 12 extra hours. At this production rate, the NPV is $581,840,400, an approximate 20% increase from the original NPV of $488,895,200. Therefore, this analysis suggests that optimizing the batch time can potentially increase the profitability of this process. Future efforts should focus on finding more efficient drying practices, scheduling optimized batch function, and reducing heating and cooling times in the vessel. However, this current economic analysis achieves the target goal of 100 kg batches with at least a 20% IRR.

Section 22: Conclusions and Recommendations

Through rigorous profitability analysis, this batch process design is determined to have an NPV of $489 million, an ROI of 400.53% and IRR of 331.79% by 2031. Since this process is profitable, and it satisfies the production demand of at least 100 kg of API per batch, we recommend that Johnson & Johnson pursue our process design according to the optimization and procedures we have discussed in the report.

Before this process design can be fully implemented, we recommend that laboratory-scale tests be performed on all steps in the process in order to validate the optimal conditions we have designed. In particular, lab-scale trials of the second-order reaction, solvent swap distillation, dry seed crystallization, and filtration and drying should be conducted and the data verified. Due to the confidential nature of this process, various assumptions were made in the calculations, such as the heat of reaction and the density of the API, that should be verified by J&J engineers. These assumptions could affect the models and the results we have devised. In addition, the true market scope and its target customers, the details of which were confidential, should be considered as high priority before making a final decision on the location of the facility. Lastly, the profitability analysis does not take into consideration research and development costs, clinical trials, and FDA approval associated with putting a pharmaceutical product on the market. These values would considerably affect the NPV, ROI, and IRR if included. Further optimization in order to make the process more profitable involves increasing the production rate by decreasing operating time. This could potentially consist of installing a second reaction vessel and filter dryer or optimizing the conditions of the filter dryer to decrease the time needed for drying.

From our analysis of the profitability and feasibility of this batch process, we believe that this process has the potential to produce Halfaxia on a scale necessary to satisfy patient demand.

Section 24: Acknowledgments

We would like to thank Dr. Wattenbarger for all of her help throughout this semester in helping us stay organized and complete our project successfully. Also, we would like to thank Professor Bruce Vrana for his thoughtful feedback on our financial analysis and helping us with report guidelines. We would also like to thank Dr. Alex Marchut for proposing this project and providing us with useful guidelines and insights into how to approach this process. Additionally, we would like to thank Professor Fabiano for his tremendous assistance in conducting batch separation simulations in Aspen. Lastly, we are extremely grateful for all of the help and guidance received by the industrial consultants throughout this semester.

Section 24: Bibliography

[1] Cancer Statistics. (2018, April 27). Retrieved April 5, 2020, from https://www.cancer.gov/about-cancer/understanding/statistics

[2] Boyes, W. (2010). *Instrumentation reference book* (4th ed.). Amsterdam: Butterworth-Heinemann/Elsevier. doi: https://doi.org/10.1016/B978-0-7506-8308-1.00035-8

[3] Active Pharmaceutical Ingredient Market Size, Share & Trends Analysis Report By Type of Synthesis (Biotech, Synthetic), By Type of Manufacturer (Captive, Merchant), By Type, By Application, By Region, And Segment Forecasts, 2020 - 2027. (2020). *Grand View Research*, 130.

[4] Future, M. R. (2018, October 4). Cancer API Market 2018 to 2023 with Leading Vendors as Exelixis, Pfizer, AstraZeneca, Ariad Pharmaceuticals and More by MRFR. Retrieved April 5, 2020, from https://www.medgadget.com/2018/10/cancer-api-market-2018-to-2023-with-leading-vendors-as-exelixis-pfizer-astrazeneca-ariad-pharmaceuticals-and-more-by-mrfr.html

[5] Active pharmaceutical Ingredient production is a high tech, high stakes business. (n.d.). Retrieved April 5, 2020, from https://www.teva-api.com/news-lobby/producing-active-pharmaceutical-ingredients-is-a-high-tech-high-stakes-business/

[6] Active Pharmaceutical Ingredient Market Size, Share & Trends Analysis Report By Type of Synthesis (Biotech, Synthetic), By Type of Manufacturer (Captive, Merchant), By Type, By Application, By Region, And Segment Forecasts, 2020 - 2027. (2020). *Grand View Research*, 130.

[7] Stone, K. (2019, November 5). What Is an Active Pharmaceutical Ingredient in Medication? Retrieved April 5, 2020, from https://www.verywellhealth.com/api-active-pharmaceutical-ingredient-2663020

[8] Leeson, P. & Springthorpe, B. (2007, November). The Influence on Drug-like Concepts on Decision-Making in Medicinal Chemistry. *Nature Reviews Drug Discovery.* Retrieved April 12, 2020, from https://www.nature.com/articles/nrd2445

[9] Mettler-Toledo International Inc. (2018, June 4). Seeding Studies For Crystallization. Retrieved April 14, 2020, from https://www.mt.com/us/en/home/applications/L1_AutoChem_Applications/L2_Crystallization/seeding-cryz.html

[10] Mayo, J. (2014, November 6). Understanding the Nutsche Filtration and Drying Process. Retrieved April 12, 2020, from https://www.ddpsinc.com/blog-0/understanding-the-nutsche-filtration-and-drying-process

[11] Warren, S. D. (2019). *Product and Process Design Principles*. S.l.: JOHN WILEY & SONS.

[12] Pressure Vessel Size Chart. (2020) *Bulldog Steel Productions, Inc.* Retrieved April 14, 2020, from https://www.bulldogsteel.com/pressure-vessel-size-chart.html

[13] Ahn, H. (2014). PHARMACEUTICAL INVENTIONS, INNOVATIONS & PRODUCTS. In *Second Generation Patents in Pharmaceutical Innovation* (pp. 28-58). Baden-Baden: Nomos Verlagsgesellschaft mbH. Retrieved April 14, 2020, from www.jstor.org/stable/j.ctv941t5f.5

[14] Pharmaceutical Process Engineer Average Salary in India 2020. (2020) *Salary Explorer*. Retrieved April 14, 2020, from http://www.salaryexplorer.com/salary-survey.php?loc=100&loctype=1&job=6129&jobtype=3

[15] Koch, M., Stoye, J., & Stahl, H. Flexible Pharma Containment Solutions. (2007). *Innovations in Pharmaceutical Technology.* Retrieved April 20, 2020, from http://iptonline.com/articles/public/IPT14passwordprotect.pdf

Section 25: Appendix

25.1 Project Statement

Batch Production of a Potent Small Molecule Active Pharmaceutical Ingredient (Recommended by Alex Marchut, Janssen Biopharmaceuticals Division of J&J)

Background

This project has been formulated to provide a pharmaceutical design project experience, using actual kinetic data for the chemical reactions and other data to produce a competitive pharmaceutical product - without identifying the Active Pharmaceutical Ingredient (API), hypothetically named Halfaxia. This problem statement identifies the principal design steps. Data will be provided for design of the process.

Most small molecule APIs are chemically synthesized in large batches, on the order of 100 kg. The Critical Quality Attributes, CQAs, are typically the chemical purity of the API and its physical properties such as solid form and particle size. A process to make the API could be as simple as a homogeneous liquid reaction followed by direct crystallization or as complex as a heterogeneous reaction sensitive to oxygen or water followed by an extraction, distillation, and finally crystallization. In both cases, filtration and drying are also used and, depending on the crystallization process and particle size requirements, sometimes a final milling step is added.

New small molecule API manufacturing facilities must be constructed so that they are flexible enough to handle both the simple and complex processes as well as anything in between. In addition, many APIs present hazards to human health in the case of occupational exposure to large quantities, so API facilities must be designed so that the equipment operators are protected from exposure to the API and manual handling of the API is kept to a minimum. Lastly, modern facilities are typically built with a good deal of automation so that paper batch records are not required, and data is automatically gathered electronically.

Project Statement

You will be working on a project where you must design a process to synthesize Halfaxia, a new potent anti-cancer API and design the production facility in which it will be manufactured. In particular, the solvent that the reaction takes place in is known (it is THF) and cannot be changed, and the solvent that the crystallization takes place in is also known (it is denatured ethanol) and cannot be changed. Other than that, you are free to design all the processing steps and conditions (for example you should optimize the reaction temperature to fully react as much starting material to product as possible, based on the kinetics that you will be given).

Once you have designed the process, you will need to design the manufacturing facility, keeping in mind all the constraints mentioned in the background. One important thing to consider is this API is not a controlled substance and the company does not foresee needing to produce controlled substances in the future, so you will not need to consider these issues in your design of the facility.

Lastly, the solvents that you will be working with in the process are flammable, hazardous, potentially corrosive to some materials, and have the potential to be volatile organic

pollutants to the atmosphere. You will need to design a facility that is safe enough to handle these and minimize their release into the atmosphere.

As you design the facility, you should do your best to keep capital costs of the equipment and operating costs of the facility to a minimum. The costs of the raw materials and product are confidential, but it will be important for you to calculate and minimize the costs of both the capital investment and the daily operation of the facility.

You can build the plant anywhere in the world, but you should consider things like cost of labor and availability of dependable supplies of utilities such as electricity and water when you choose the location.

For purposes of your design, you will be given an approximate raw material starting cost and an approximate selling price of the API in its dried but unformulated state. From these prices and your capital and operating cost estimates for this part of the manufacturing process, you should seek to optimize the NPV of the process, assuming your company needs to earn at least a 20% IRR on the investment. Although estimated to be in the billions of dollars, you do not need to include the initial cost of clinical trials and FDA registration in your economics, as it is included in the economics for the final formulated product, which are confidential.

25.2 Design Calculations

25.2.1 Production of API in THF

For a 1st order batch reaction:

$$A \rightarrow P$$

$$C_{Ao}\frac{dx_A}{dt} = kC_A$$

$$-\ln(1 - x_A) = kt$$

$$x_A = 1 - e^{-kt}$$

x_A: conversion of A

t: time

$k\ \left[\frac{L \cdot mol}{s}\right]$: rate constant at 50 C

Given Kinetic Information

$$k\left[\frac{L}{mol \cdot s}\right] = 2.91 \cdot 10^{-4} e^{\frac{8.95}{RT}}$$

$$At\ T = 50\ ℃, rate\ constant\ k = 2.90 \times 10^{-4}\ \frac{L}{mol \cdot s}$$

$$if\ x_A = 0.998 = 1 - e^{-(2.90 \times 10^{-4})t}$$

$$\boldsymbol{t = 6\ hours\ to\ achieve\ 99.8\%\ conversion}$$

Finding Final Concentration of Starting Material

$$\frac{1}{C_A} - \frac{1}{C_{AO}} = kt$$

$$\frac{1}{C_A} - \frac{1}{87.1} = (2.90 \times 10^{-4})(6 \times 3600)$$

$$\boldsymbol{C_A = 0.17\ \frac{mg}{mL}}$$

25.2.2 Crystallization

Solubility Curve information of API in Ethanol

$$Solubility\ \left(\frac{mg}{mL}\right) = 4.43e^{0.0365T}$$
$$T = ℃$$
$$Concentration\ of\ API\ at\ 80\ ℃ = 80.38\frac{mg}{ml}$$
$$Saturated\ Solubility\ of\ API\ at\ 80\ ℃ = 4.43e^{0.0365(80)} = 82.13\frac{mg}{mL}$$

In order to achieve supersaturation, must at least hit the saturated solubility of API

$$Temperature\ Required\ for\ Saturation: 80.38 = 4.43e^{0.0365(T)}$$
$$\boldsymbol{T = 79.4}\ ℃$$

Determining Mass of Dry Seed to Add

$$Mass\ of\ Dry\ Seed\ Added = 0.01 * Final\ Mass\ of\ Product = 0.01 * (100kg)$$
$$= \mathbf{1\ kg\ dry\ seed}$$

Determining Operating Time of Crystallization

Hold at initial temperature for three hours, cool from initial temp to final temp at a rate of 5 ℃/hr

$$time = 3\ hr + \frac{80\ ℃ - 5\ ℃}{5\ ℃/hr} = \mathbf{18\ hours}$$

25.2.3 Pump Design

Example Calculation for THF Pump: P-100

$$Head = \frac{Pressure\ Change}{Fluid\ Density} = \frac{\Delta P}{\rho} = \frac{44.1\ psi * \frac{144 in^2}{ft^2}}{55.43 \frac{lb}{ft^3}} = 115\ ft = \mathbf{35.05\ m}$$

$$Pump\ Efficiency = \ \eta_p = -0.316 + 0.24015 \ln(Q) - 0.0119(\ln\ (Q))^2$$

$$For\ Q = 317 gal/\min = \mathbf{20\ L/s}$$

$$\boldsymbol{\eta_p = 0.67}$$

$$P_B = \frac{QH\rho}{33{,}000\eta_p} = \frac{(317 \times 115 \times 7.41\ lb/gal)}{(33{,}000 \times 0.67)} = 12.23\ hp$$

$$n_M = 0.80 + 0.0319 \ln(P_B) - 0.00182(\ln\ (P_B))^2$$

$$n_M = 0.87$$

$$P_C = \frac{P_B}{n_M} = \mathbf{14.05\ hp}$$

Total Electricity Required Per Batch

$$Electricity = \ P_C \times \ Operating\ Time$$

$$Total\ Mass\ of\ THF: 2042.4\ kg\ per\ batch$$

$$Electricity = 14.05\ hp\ \times \frac{0.7456\ kW}{1\ hp} \times \left(\frac{2042.29\ kg}{20 \frac{kg}{s}}\right) \times \frac{1\ hr}{3600\ sec} = \mathbf{0.300\ kWh}$$

25.2.4 Jacket Heat Duty and Flow Rate

For all operational steps involving a change in temperature of the vessel (R-100) excluding the solvent swap step, an energy balance was used to calculate the temperature of the vessel contents as a function of time. Assuming that the jacket fluid temperature is constant, the following differential energy balance can be applied between the jacket fluid and vessel contents:

$$Q = UA(T_j - T_v) = m_v C_{p,v} \frac{dT_v}{dt}$$

U is the overall heat transfer coefficient, A is the heat transfer area, T_j is the is the temperature of the vessel, m_v is the mass of the vessel contents, $C_{p,\,avg}$ is the average heat capacity of the vessel contents, and T_v is the temperature of the vessel contents. The overall heat transfer coefficient is dependent on the flow characteristics and thermodynamic properties of the vessel contents and jacket fluid, as well as the properties of the stainless steel wall and glass lining. In the initial calculations, an estimated U value is used, and this value is later adjusted based on the jacket flow rate and temperature that is to be calculated. The heat transfer area A is a function of the volume present in the reactor. The maximum heat transfer area is 11.7 m^2, and it was estimated based on the height of the jacket that the maximum heat transfer area is reached when the volume of the vessel reaches 3700 L. Based on these values, following equation for heat transfer area as a function of volume of vessel contents was derived:

$$A = 1.3 \times (\frac{V}{1.15})^{2/3}$$

V is the volume of the vessel contents. $C_{p,\,v}$ is dependent on the composition and temperature range of the vessel contents and was evaluated for each operational step based on property data.

With these values, the differential energy balance was solved to find the temperature of the vessel contents as a function of time. Because the time frame for each step had been

determined previously, the temperature of the jacket was adjusted such that the temperature change can occur within the desired time frame.

Based on the temperature time profile, the heat duty for each time increment was calculated using the following equation:

$$Q = \frac{m_v C_{p,v} \Delta T}{\Delta t}$$

Q is the heat duty, Δt is the time increment, and the ΔT is the change in temperature that occurs during that time increment.

The heat duty was then used to calculate the required flow rate of jacket fluid that supplies the heat duty. The following equation was solved for the flow rate of jacket fluid:

$$Q = \dot{m}_J C_{p,j} (T_{j,o} - T_{j,i})$$

The $\dot{m}_J$ is the mass flow rate of the jacket fluid, $C_{p,j}$ is the average heat capacity of the jacket fluid, and $T_{j,o}$ and $T_{j,i}$ are the temperatures of the jacket fluid out of and in to the jacket, respectively. Although it was initially assumed that the jacket fluid temperature is constant, a temperature change must be assumed to calculate the flow rate of jacket fluid. As such, a moderate temperature change of 5 °C was assumed.

Based on the flow rate of the jacket fluid calculated above, the actual *U* value now be calculated. First empirical correlations developed by Lehrer (1970) for conventional unbaffled jackets with liquid service with high flow was used to calculate the heat transfer coefficient of the jacket side.[1] The following equations were used:

$$Nu_j = \frac{0.03 {Re_j}^{3/4} Pr_j}{1 + 1.74 {Re_j}^{-\frac{1}{8}} (Pr_j - 1)}$$

$$Re_j = \frac{d_e \rho (\sqrt{v_v v_A} + v_B)}{\mu}$$

[1] Lehrer, I. H. (1970). Jacket-Side Nusselt Number. *Industrial & Engineering Chemistry Process Design and Development*, *9*(4), 553–558. doi: 10.1021/i260036a010

$$d_e = 0.816(D_j - D_v)$$

$$v_i = \frac{4\dot{V}}{\pi {d_i}^2}, v_B = 0.5\sqrt{2z\beta\left|T_{j,o} - T_{j,i}\right|}$$

Re_j, Pr_j, and Nu_j are the Reynolds, Prandtl, and Nusselt numbers associated with the jacket flow, respectively. ρ and μ correspond to the density and viscosity of the jacket fluid. d_e is the characteristic length associated with the jacket. v_i is the velocity at the inlet nozzle and v_B is the velocity component due to buoyancy. D_j is the jacket diameter, and D_v is the vessel diameter. $\dot{V}$ is the volumetric flow rate of the jacket fluid, d_i is the diameter of the inlet, z is the wetted height of the jacket, β is the fluid thermal expansion coefficient. v_A is the rise velocity in the jacket annulus and depends on the inlet orientation, which was assumed to be radially oriented:

$$v_A = \frac{4\dot{V}}{\pi({D_j}^2 - {D_v}^2)}$$

According to the specifications for the vessel in Section 16, D_j is 1.9m, D_v is 1.8m, and d_i is 52.5 mm. $\dot{V}$ was calculated based on the mass flow rate of the jacket fluid and the density of 30% w/w ethylene glycol at the desired temperatures. z was assumed to be approximately 1.5 m based on the dimensions of the jacket. β was calculated using the following equation:

$$\beta \cong \frac{1}{V}\left(\frac{\Delta V}{\Delta T}\right)$$

Using these equations, Nu_j was acquired. $Nu_j$was then used to calculate the heat transfer coefficient h_j for the jacket fluid using the following equation:

$$h_j = \frac{Nu_j * k_j}{d_e}$$

k_j is the thermal conductivity of the jacket fluid.

For the vessel-side heat transfer coefficient, the following correlations developed by Vitor da Silva Rosa and Deovaldo de Moraes Júnior were used.[2]

$$Re_v = N \frac{* {d_{imp}}^2 * \rho}{\mu}$$

$$Nu_v = 0.36 {Re_v}^{2/3} {Pr_v}^{1/3}$$

Re_v, Pr_v, and Nu_v are the Reynolds, Prandtl, and Nusselt numbers associated with the vessel side, respectively. ρ and μ correspond to the density and viscosity of the vessel contents. The *N* is the rotational speed of the agitator, which corresponds to 50 rpm. d_{imp} is the length of the agitator, or tip-to-center length, which is 1.1m. Using the length of the agitator, the rotational speed was calculated to be 2.9 m/s at the tip of the agitator. Using these equations, Nu_v was acquired. Nu_v was then used to calculate the heat transfer coefficient h_j for the jacket fluid using the following equation:

$$h_v = \frac{Nu_v * k_v}{d_{imp}}$$

k_v is the thermal conductivity of the jacket fluid.

Finally the overall heat transfer coefficient *U* can be calculated by the following equations:

$$U = \frac{1}{\frac{1}{h_j} + \left(R_{wall} + R_{lining}\right) + \frac{1}{h_v}}$$

$$R_{wall} = \frac{L_{wall}}{k_{wall} A}, R_{lining} = \frac{L_{lining}}{k_{lining} A}$$

R_{lining} and R_{wall} are the thermal resistance of the stainless-steel wall and glass lining. According to the specifications of the vessel in Section 16, L_{wall} and k_{wall} are 20 mm and 40 W/m-K, respectively, and L_{lining} and k_{lining} are 1mm and 1.5 W/m-K, respectively.

[2] Rosa, V. D. S., & Júnior, D. D. M. (2017). Design of Heat Transfer Surfaces in Agitated Vessels. *Heat Exchangers - Design, Experiment and Simulation*. doi: 10.5772/66729

After *U* is calculated from the correlations, it is compared to the initial estimated *U* used to calculated the heat duty. If they do not match, the estimated *U* is adjusted, which subsequently changes the required jacket fluid flow rate. Because the flow rate changed, the *U* calculated from the correlations also changes. By trial and error, the estimated U value is adjusted until it agrees with the *U* calculated from the correlations, which then allow the correct heat duty and jacket flow rates to be acquired. The average heat duty and jacket flow rate for for each operational step was calculated in this manner, and the results are tabulated in Table 14.1.1 to 14.1.3.

25.2.5. Jacket Heat Duty and Flow Rate for Distillation

One exception to the calculations described in Section 25.2.3 is for the distillation phase, where the solvent is swapped from THF to ethanol over approximately 19 hours. Unlike other operational steps where the energy balance could be done by hand, this step required modeling on ASPEN using the BATCHSEP block due to the distillation and addition of ethanol changing the composition and volume of the vessel contents throughout the process. Instead of solving an unsteady state energy balance as in Section 25.2.3 to acquire the temperature as a function of time, the time profile data from ASPEN was used directly to find both the temperature of the vessel contents and the heat duty as a function of time.

Two inputs needed to be optimized: the overall heat transfer coefficient and the rate of ethanol addition. For the ASPEN simulation, a estimated overall heat transfer coefficient was used, and based on the heat duty as a function of time, the same procedure as outlined in Section 25.2.3 was employed such that the estimated overall heat transfer coefficient and that calculated from the correlations agree with one another. The resulting overall heat transfer coefficient was 330 W/m^2-K. The rate of ethanol addition was then adjusted such that the vessel contents do not exceed the maximum capacity of the vessel during the distillation. Through an iterative process, it was determined that the fastest rate of ethanol addition after the initial batch of 1171 kg over 0.5 hours was 410 kg/hr over 14 hours. Increasing the flow rate would decrease the total time for distillation, but the overall heat transfer coefficient is not high enough to provide the required heat duty, and the volume of the vessel contents exceed the maximum capacity of the vessel. The ASPEN inputs and results are available in Section 25.4.

25.2.6 Heat Exchanger Sizing and Utility Requirements

The steam and water heat exchangers were used to replenish or take away heat from the jacket fluid as necessary for each operational step. As such they were designed to accommodate the largest heat duty requirements of each process. The following energy balance equations were used:

$$Q = \dot{m}_j C_{p,j}\left(T_{j,o} - T_{j,i}\right) = U_{ex} A_{ex} \Delta T_{lm}$$

$$\Delta T_{lm} = \frac{\left(T_{j,o} - T_{u,i}\right) - \left(T_{j,i} - T_{u,o}\right)}{\ln\left(\frac{T_{j,o} - T_{u,i}}{T_{j,i} - T_{u,o}}\right)}$$

Q is the heat duty between the jacket fluid and heat exchanger, $\dot{m}_j$ is the mass flow rate of the jacket fluid, and $C_{p,j}$ is the average heat capacity of the jacket fluid. $T_{j,o}$ and $T_{j,i}$ are the temperatures of the jacket fluid out of and into the heat exchanger, respectively. The flow rate and the temperature of the jacket was determined as shown in Section 25.2.4 and 25.2.5. $T_{u,o}$ and $T_{u,i}$ are the temperatures of the utility out of and into the heat exchanger, respectively. U_{ex} is the overall heat transfer coefficient of the heat exchanger. A_{ex} is the heat transfer area for the heat exchanger. ΔT_{lm} is the log mean temperature difference for the heat exchanger.

First, the heat duty was calculated for each operational step. Then the ΔT_{lm} was calculated for each operational step assuming that the utility used was low pressure steam at 50psig, or 148 °C. In this case, it is assumed that the steam fully condenses and leaves the heat exchanger as a liquid at the same temperature. Thus, $T_{u,o}$ and $T_{u,i}$ are the same. The overall heat transfer coefficient was assumed to be 750W/m^2-K, a typical value for a shell-and-tube heat exchanger with organic solvent on the tube side and steam on the shell side.[3] The aforementioned equation was then solved for A_{ex}:

[3] Page, E. (n.d.). TYPICAL OVERALL HEAT TRANSFER COEFFICIENTS (U - VALUES). Retrieved from https://www.engineeringpage.com/technology/thermal/transfer.html

$$A_{ex} = \frac{\dot{m}_j C_{p,j}\left(T_{j,o} - T_{j,i}\right)}{U_{ex}\Delta T_{lm}}$$

The calculated A_{ex} was different for each operational step. The maximum value, 6 m^2, was then selected as the heat transfer area of the steam heat exchanger.

This also meant that the temperature of the utilities must be changed for the other operational steps where the required A_{ex} was smaller than the maximum value. If the same steam at 148 °C was used, then the heat duty would be excessively large and cause a greater than desired temperature for the jacket fluid. A new ΔT_{lm} was calculated for each step, and the new temperature of the steam required was found. The latent heat of vaporization was acquired from steam tables for each temperature of steam that was calculated, and the following equation was used to calculate the flow rate of steam required.

$$Q = \dot{m}_s \Delta h_{vap}$$

$\dot{m}_s$ is the flow rate of the steam, and Δh_{vap} is the latent heat of vaporization. The differing temperatures and flow rates of the steam required for each operational step are tabulated in Table 14.1.1.

If the required temperature of the utility turned out to be less than 100 °C, this indicated that the heat duty required for that operational step was too small to be supplied by steam. In this case, the heating was performed using the water heat exchanger, along with the cooling steps required for crystallization. The sizing of the water heat exchanger was performed in the same manner. In this case, temperature of the water was initially assumed to be 90 °C, such that $T_{u,o}$ and $T_{u,i}$ were 85 °C and 90 °C for the heating steps. For the cooling steps, temperature of the water was initially assumed to be 5 °C, such that $T_{u,o}$ and $T_{u,i}$ were 10 °C and 5 °C. A_{ex} was again calculated for each operational step, and the maximum area was calculated to be approximately 9.3m^2. This was rounded to 10 m^2, which was chosen as the heat transfer area of the water heat exchanger. For all steps, the new ΔT_{lm} was calculated for

each step, and the new temperature of the water required was found. The flow rate of the water required was calculated using the following equation:

$$Q = \dot{m}_w C_{p,w}\left(T_{w,o} - T_{w,i}\right)$$

$\dot{m}_w$ is the flow rate of the water, and $C_{p,w}$ is the heat capacity of the water. $T_{w,o} - T_{w,i}$ was assumed to be 5 °C for heating steps and -5 °C for cooling steps. The differing temperatures and flow rates of the water required for each operational step are tabulated in Table 14.1.1. to 14.1.3.

The above steps were repeated for the condenser, which was also modeled on ASPEN using the BATCHSEP block. In this case, the heat duty as a function of time during the distillation was found via the simulation, and the above process was used to determine the maximum A_{ex} required for the largest heat duty to the condenser during the distillation, assuming cooling water at 20 °C was used as the cold fluid.

25.2.7 Horizontal Pressure Vessel Design

Table 25.2.7.1: Ethanol and THF Horizontal Pressure Vessel Design

Compound	Amount required per batch (kg)	Amount required per batch (gal)	Amount required per 3 batches (gal)	Tanker truck size required (gal)	Pressure Vessel Volume (gal)
Ethanol	7058	2363	7089	7500	12000
THF	2042	607	1821	2500	4000

Table 25.2.7.2: Distillate and Mother Liquor Horizontal Pressure Vessel Design

Compound	Amount generated per batch (kg)	Amount generated per batch (gal)	Amount generated per 3 batches (gal)	Tanker truck size required (gal)	Pressure Vessel Volume (gal)
Distillate	7126	2310	6930	7500	12000
Mother Liquor	1846	631	1893	2500	4000

25.3 Safety Data Sheets

Fisher Scientific
Part of Thermo Fisher Scientific

SAFETY DATA SHEET

Creation Date 11-Jun-2009 **Revision Date** 09-Feb-2016 **Revision Number** 2

1. Identification

Product Name **Tetrahydrofuran**

Cat No. : **BP1140-1**

Synonyms THF

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Emergency Telephone Number
Chemtrec US: (800) 424-9300
Chemtrec EU: 001 (202) 483-7616

2. Hazard(s) identification

Classification
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Flammable liquids	Category 2
Acute oral toxicity	Category 4
Serious Eye Damage/Eye Irritation	Category 2
Carcinogenicity	Category 2
Specific target organ toxicity (single exposure)	Category 3
Target Organs - Respiratory system, Central nervous system (CNS).	

Label Elements

Signal Word
Danger

Hazard Statements
Highly flammable liquid and vapor
Harmful if swallowed
Causes serious eye irritation
May cause respiratory irritation
May cause drowsiness or dizziness
Suspected of causing cancer

Precautionary Statements
Prevention
Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Use personal protective equipment as required
Wash face, hands and any exposed skin thoroughly after handling
Do not eat, drink or smoke when using this product
Wear eye/face protection
Do not breathe dust/fume/gas/mist/vapors/spray
Use only outdoors or in a well-ventilated area
Keep away from heat/sparks/open flames/hot surfaces. - No smoking
Keep container tightly closed
Ground/bond container and receiving equipment
Use explosion-proof electrical/ventilating/lighting/equipment
Use only non-sparking tools
Take precautionary measures against static discharge
Keep cool
Response
IF exposed or concerned: Get medical attention/advice
Inhalation
IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing
Skin
IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower
Eyes
IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
If eye irritation persists: Get medical advice/attention
Ingestion
IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell
Rinse mouth
Fire
In case of fire: Use CO2, dry chemical, or foam for extinction
Storage
Store locked up
Store in a well-ventilated place. Keep container tightly closed
Disposal
Dispose of contents/container to an approved waste disposal plant
Hazards not otherwise classified (HNOC)
May form explosive peroxides

3. Composition / information on ingredients

Component	CAS-No	Weight %
Tetrahydrofuran	109-99-9	>95

4. First-aid measures

General Advice If symptoms persist, call a physician.

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Obtain medical attention.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. If skin irritation persists, call a physician.

Inhalation Move to fresh air. If not breathing, give artificial respiration. Get medical attention if symptoms occur.

Ingestion Clean mouth with water and drink afterwards plenty of water.

Most important symptoms/effects . Symptoms of overexposure may be headache, dizziness, tiredness, nausea and vomiting: Causes central nervous system depression

Notes to Physician Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide. Cool closed containers exposed to fire with water spray.

Unsuitable Extinguishing Media Water may be ineffective

Flash Point -21 °C / -5.8 °F

Method - No information available

Autoignition Temperature 215 °C / 419 °F

Explosion Limits

Upper 11.8%

Lower 2.0%

Sensitivity to Mechanical Impact No information available

Sensitivity to Static Discharge No information available

Specific Hazards Arising from the Chemical

Flammable. Containers may explode when heated. Vapors may form explosive mixtures with air. Vapors may travel to source of ignition and flash back. May form explosive peroxides.

Hazardous Combustion Products

Carbon monoxide (CO) Carbon dioxide (CO_2) peroxides

Protective Equipment and Precautions for Firefighters

As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
2	3	1	N/A

6. Accidental release measures

Personal Precautions Use personal protective equipment. Ensure adequate ventilation. Remove all sources of ignition. Take precautionary measures against static discharges.

Environmental Precautions Should not be released into the environment.

Methods for Containment and Clean Up Soak up with inert absorbent material. Keep in suitable, closed containers for disposal. Remove all sources of ignition. Use spark-proof tools and explosion-proof equipment.

7. Handling and storage

Handling Wear personal protective equipment. Do not get in eyes, on skin, or on clothing. Ensure adequate ventilation. Avoid ingestion and inhalation. If peroxide formation is suspected, do not open or move container. Keep away from open flames, hot surfaces and sources of ignition. Use only non-sparking tools. To avoid ignition of vapors by static electricity discharge, all metal parts of the equipment must be grounded. Take precautionary measures against static discharges.

Storage Shelf life 6 months. May form explosive peroxides on prolonged storage. Containers should be dated when opened and tested periodically for the presence of peroxides. Should crystals form in a peroxidizable liquid, peroxidation may have occurred and the product should be considered extremely dangerous. In this instance, the container should only be opened remotely by professionals. Keep containers tightly closed in a dry, cool and

well-ventilated place. Keep away from heat and sources of ignition. Flammables area. Store under an inert atmosphere.

8. Exposure controls / personal protection

Exposure Guidelines

Component	ACGIH TLV	OSHA PEL	NIOSH IDLH	Mexico OEL (TWA)
Tetrahydrofuran	TWA: 50 ppm STEL: 100 ppm Skin	(Vacated) TWA: 200 ppm (Vacated) TWA: 590 mg/m³ (Vacated) STEL: 250 ppm (Vacated) STEL: 735 mg/m³ TWA: 200 ppm TWA: 590 mg/m³	IDLH: 2000 ppm TWA: 200 ppm TWA: 590 mg/m³ STEL: 250 ppm STEL: 735 mg/m³	TWA: 200 ppm TWA: 590 mg/m³ STEL: 250 ppm STEL: 735 mg/m³

Legend

ACGIH - *American Conference of Governmental Industrial Hygienists*
OSHA - *Occupational Safety and Health Administration*
NIOSH IDLH: *The National Institute for Occupational Safety and Health Immediately Dangerous to Life or Health*

Engineering Measures Use explosion-proof electrical/ventilating/lighting/equipment. Ensure that eyewash stations and safety showers are close to the workstation location. Ensure adequate ventilation, especially in confined areas.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Long sleeved clothing.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Liquid
Appearance	Colorless
Odor	Petroleum distillates
Odor Threshold	No information available
pH	7-8 20% aq. solution
Melting Point/Range	-108.4 °C / -163.1 °F
Boiling Point/Range	66 °C / 150.8 °F
Flash Point	-21 °C / -5.8 °F
Evaporation Rate	> 1 (Ether = 1.0)
Flammability (solid,gas)	Not applicable
Flammability or explosive limits	
Upper	11.8%
Lower	2.0%
Vapor Pressure	200 mbar @ 20 °C
Vapor Density	2.5 (Ether = 1.0)
Specific Gravity	0.880
Solubility	miscible
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	215 °C / 419 °F
Decomposition Temperature	No information available

Viscosity	0.55 cP @ 20 °C
Molecular Formula	C4H8O
Molecular Weight	72.11

10. Stability and reactivity

Reactive Hazard Yes.

Stability May form explosive peroxides. Hygroscopic.

Conditions to Avoid Incompatible products. Excess heat. Keep away from open flames, hot surfaces and sources of ignition. Exposure to moist air or water.

Incompatible Materials Strong oxidizing agents, Acids

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2), peroxides

Hazardous Polymerization Hazardous polymerization may occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Tetrahydrofuran	1650 mg/kg (Rat)	> 2000 mg/kg (Rabbit)	180 mg/L (Rat) 1 h 53.9 mg/L (Rat) 4 h

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation Irritating to eyes May cause irritation of respiratory tract

Sensitization No information available

Carcinogenicity Limited evidence of a carcinogenic effect.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Tetrahydrofuran	109-99-9	Not listed	Not listed	A3	Not listed	Not listed

ACGIH: (American Conference of Governmental Industrial Hygienists)

A1 - Known Human Carcinogen
A2 - Suspected Human Carcinogen
A3 - Animal Carcinogen
ACGIH: (American Conference of Governmental Industrial Hygienists)

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure Respiratory system Central nervous system (CNS)

STOT - repeated exposure None known

Aspiration hazard No information available

Symptoms / effects,both acute and delayed Symptoms of overexposure may be headache, dizziness, tiredness, nausea and vomiting: Causes central nervous system depression

Endocrine Disruptor Information

Component	EU - Endocrine Disrupters Candidate List	EU - Endocrine Disruptors - Evaluated Substances	Japan - Endocrine Disruptor Information
Tetrahydrofuran	Group III Chemical	Not applicable	Not applicable

Other Adverse Effects Tumorigenic effects have been reported in experimental animals.

12. Ecological information

Ecotoxicity

Do not empty into drains. .

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Tetrahydrofuran	Not listed	2160 mg/l LC50 = 96 h Pimephales promelas Leuciscus idus: LC50: 2820 mg/L/48h	Not listed	EC50 48 h 3485 mg/l EC50: >10000 mg/L/24h

Persistence and Degradability Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its volatility.

Component	log Pow
Tetrahydrofuran	0.45

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

Component	RCRA - U Series Wastes	RCRA - P Series Wastes
Tetrahydrofuran - 109-99-9	U213	-

14. Transport information

DOT

UN-No UN2056
Proper Shipping Name TETRAHYDROFURAN
Hazard Class 3
Packing Group II

TDG

UN-No UN2056
Proper Shipping Name TETRAHYDROFURAN
Hazard Class 3
Packing Group II

IATA

UN-No UN2056
Proper Shipping Name TETRAHYDROFURAN
Hazard Class 3
Packing Group II

IMDG/IMO

UN-No UN2056
Proper Shipping Name TETRAHYDROFURAN
Hazard Class 3
Packing Group II

15. Regulatory information

All of the components in the product are on the following Inventory lists: X = listed

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Tetrahydrofuran	X	X	-	203-726-8	-		X	X	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b)

Component	TSCA 12(b)
Tetrahydrofuran	Section 4, 1 % de minimus concentration

SARA 313 Not applicable

SARA 311/312 Hazard Categories

Acute Health Hazard	Yes
Chronic Health Hazard	Yes
Fire Hazard	Yes
Sudden Release of Pressure Hazard	No
Reactive Hazard	Yes.

CWA (Clean Water Act) Not applicable

Clean Air Act Not applicable

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA
This material, as supplied, contains one or more substances regulated as a hazardous substance under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (40 CFR 302)

Component	Hazardous Substances RQs	CERCLA EHS RQs
Tetrahydrofuran	1000 lb	-

California Proposition 65 This product does not contain any Proposition 65 chemicals

U.S. State Right-to-Know Regulations

Component	Massachusetts	New Jersey	Pennsylvania	Illinois	Rhode Island
Tetrahydrofuran	X	X	X	-	X

U.S. Department of Transportation

Reportable Quantity (RQ):	Y
DOT Marine Pollutant	N
DOT Severe Marine Pollutant	N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade	Serious risk, Grade 3

16. Other information

Prepared By	Regulatory Affairs Thermo Fisher Scientific Email: EMSDS.RA@thermofisher.com
Creation Date	11-Jun-2009
Revision Date	09-Feb-2016
Print Date	09-Feb-2016
Revision Summary	This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 09-Jul-2009 **Revision Date** 18-Jan-2018 **Revision Number** 4

1. Identification

Product Name Ethanol, Anhydrous (Histological)

Cat No. : A405-20; A405F-1GAL; A405P-4

Synonyms Grain alcohol, denatured; Ethyl alcohol, denatured; Ethyl hydroxide, denatured.

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Flammable liquids	Category 2
Serious Eye Damage/Eye Irritation	Category 2
Specific target organ toxicity (single exposure)	Category 1
Target Organs - Central nervous system (CNS), Optic nerve, Respiratory system.	
Specific target organ toxicity - (repeated exposure)	Category 1
Target Organs - Kidney, Liver, spleen, Blood.	

Label Elements

Signal Word
Danger

Hazard Statements
Highly flammable liquid and vapor
Causes serious eye irritation
Causes damage to organs
Causes damage to organs through prolonged or repeated exposure

Precautionary Statements
Prevention
Obtain special instructions before use
Do not handle until all safety precautions have been read and understood
Use personal protective equipment as required
Wash face, hands and any exposed skin thoroughly after handling
Wear eye/face protection
Do not breathe dust/fume/gas/mist/vapors/spray
Do not eat, drink or smoke when using this product
Keep away from heat/sparks/open flames/hot surfaces. - No smoking
Keep container tightly closed
Ground/bond container and receiving equipment
Use explosion-proof electrical/ventilating/lighting/equipment
Use only non-sparking tools
Take precautionary measures against static discharge
Response
IF exposed: Call a POISON CENTER or doctor/physician
Skin
IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower
Eyes
IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing
If eye irritation persists: Get medical advice/attention
Fire
In case of fire: Use CO2, dry chemical, or foam for extinction
Storage
Store locked up
Store in a well-ventilated place. Keep cool
Disposal
Dispose of contents/container to an approved waste disposal plant
Hazards not otherwise classified (HNOC)
Repeated exposure may cause skin dryness or cracking
Other hazards
Poison, may be fatal or cause blindness if swallowed. Vapor harmful. Cannot be made non-poisonous.
WARNING. Cancer and Reproductive Harm - https://www.p65warnings.ca.gov/.

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Ethyl alcohol	64-17-5	91-92
Methyl alcohol	67-56-1	<5
Methylisobutyl ketone	108-10-1	1.0 - 2.0
Ethyl acetate	141-78-6	1-2
Hexane	110-54-3	<1
Toluene	108-88-3	<0.1
Ligroine	8032-32-4	<0.1

4. First-aid measures

General Advice If symptoms persist, call a physician.

Eye Contact	Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.
Skin Contact	Wash off immediately with plenty of water for at least 15 minutes. If skin irritation persists, call a physician.
Inhalation	Move to fresh air. If not breathing, give artificial respiration. Get medical attention if symptoms occur.
Ingestion	Clean mouth with water and drink afterwards plenty of water.
Most important symptoms and effects	None reasonably foreseeable. Breathing difficulties. Inhalation of high vapor concentrations may cause symptoms like headache, dizziness, tiredness, nausea and vomiting
Notes to Physician	Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media	Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Unsuitable Extinguishing Media	Water may be ineffective, Do not use a solid water stream as it may scatter and spread fire
Flash Point	13.9 °C / 57 °F
Method -	No information available
Autoignition Temperature	362.8 °C / 685 °F
Explosion Limits	
Upper	18.0 vol %
Lower	3.3 vol %
Sensitivity to Mechanical Impact	No information available
Sensitivity to Static Discharge	No information available

Specific Hazards Arising from the Chemical
Flammable. Vapors may form explosive mixtures with air. Vapors may travel to source of ignition and flash back. Containers may explode when heated. Vapors may form explosive mixtures with air.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2)
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
3	3	0	N/A

6. Accidental release measures

Personal Precautions	Use personal protective equipment. Ensure adequate ventilation.
Environmental Precautions	Should not be released into the environment. See Section 12 for additional ecological information.
Methods for Containment and Clean Up	Soak up with inert absorbent material. Keep in suitable, closed containers for disposal.

7. Handling and storage

Handling	Wear personal protective equipment. Ensure adequate ventilation. Do not get in eyes, on skin, or on clothing. Avoid ingestion and inhalation.

Storage Keep containers tightly closed in a dry, cool and well-ventilated place. Keep away from heat and sources of ignition.

8. Exposure controls / personal protection

Exposure Guidelines

Component	ACGIH TLV	OSHA PEL	NIOSH IDLH	Mexico OEL (TWA)
Ethyl alcohol	STEL: 1000 ppm	(Vacated) TWA: 1000 ppm (Vacated) TWA: 1900 mg/m³ TWA: 1000 ppm TWA: 1900 mg/m³	IDLH: 3300 ppm TWA: 1000 ppm TWA: 1900 mg/m³	TWA: 1000 ppm TWA: 1900 mg/m³
Methyl alcohol	TWA: 200 ppm STEL: 250 ppm Skin	(Vacated) TWA: 200 ppm (Vacated) TWA: 260 mg/m³ (Vacated) STEL: 250 ppm (Vacated) STEL: 325 mg/m³ Skin TWA: 200 ppm TWA: 260 mg/m³	IDLH: 6000 ppm TWA: 200 ppm TWA: 260 mg/m³ STEL: 250 ppm STEL: 325 mg/m³	TWA: 200 ppm TWA: 260 mg/m³ STEL: 250 ppm STEL: 310 mg/m³
Methylisobutyl ketone	TWA: 20 ppm STEL: 75 ppm	(Vacated) TWA: 50 ppm (Vacated) TWA: 205 mg/m³ (Vacated) STEL: 75 ppm (Vacated) STEL: 300 mg/m³ TWA: 100 ppm TWA: 410 mg/m³	IDLH: 500 ppm TWA: 50 ppm TWA: 205 mg/m³ STEL: 75 ppm STEL: 300 mg/m³	TWA: 50 ppm TWA: 205 mg/m³ STEL: 75 ppm STEL: 307 mg/m³
Ethyl acetate	TWA: 400 ppm	(Vacated) TWA: 400 ppm (Vacated) TWA: 1400 mg/m³ TWA: 400 ppm TWA: 1400 mg/m³	IDLH: 2000 ppm TWA: 400 ppm TWA: 1400 mg/m³	TWA: 400 ppm TWA: 1400 mg/m³
Hexane	TWA: 50 ppm Skin	(Vacated) TWA: 50 ppm (Vacated) TWA: 180 mg/m³ TWA: 500 ppm TWA: 1800 mg/m³	IDLH: 1100 ppm TWA: 50 ppm TWA: 180 mg/m³	TWA: 50 ppm TWA: 176 mg/m³
Toluene	TWA: 20 ppm	(Vacated) TWA: 100 ppm (Vacated) TWA: 375 mg/m³ Ceiling: 300 ppm (Vacated) STEL: 150 ppm (Vacated) STEL: 560 mg/m³ TWA: 200 ppm	IDLH: 500 ppm TWA: 100 ppm TWA: 375 mg/m³ STEL: 150 ppm STEL: 560 mg/m³	TWA: 50 ppm TWA: 188 mg/m³
Ligroine		(Vacated) TWA: 300 ppm (Vacated) TWA: 1350 mg/m³ (Vacated) STEL: 400 ppm (Vacated) STEL: 1800 mg/m³	TWA: 350 mg/m³ Ceiling: 1800 mg/m³	TWA: 300 ppm TWA: 1350 mg/m³ STEL: 400 ppm STEL: 1800 mg/m³

Legend

ACGIH *- American Conference of Governmental Industrial Hygienists*
OSHA *- Occupational Safety and Health Administration*
NIOSH IDLH: *The National Institute for Occupational Safety and Health Immediately Dangerous to Life or Health*

Engineering Measures Ensure adequate ventilation, especially in confined areas. Use explosion-proof electrical/ventilating/lighting/equipment. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Long sleeved clothing.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

Hygiene Measures Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Liquid
Appearance	Clear
Odor	Alcohol-like
Odor Threshold	No information available
pH	No information available
Melting Point/Range	< -90 °C / -130 °F
Boiling Point/Range	No information available 77.1 °C / 170.8 °F
Flash Point	13.9 °C / 57 °F
Evaporation Rate	3.6 (Butyl acetate = 1.0)
Flammability (solid,gas)	Not applicable
Flammability or explosive limits	
Upper	18.0 vol %
Lower	3.3 vol %
Vapor Pressure	48 mmHg
Vapor Density	1.5
Specific Gravity	0.785 - 0.792
Solubility	Soluble in water
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	362.8 °C / 685 °F
Decomposition Temperature	No information available
Viscosity	No information available

10. Stability and reactivity

Reactive Hazard None known, based on information available

Stability Stable under normal conditions.

Conditions to Avoid Incompatible products. Excess heat. Keep away from open flames, hot surfaces and sources of ignition.

Incompatible Materials Strong oxidizing agents, Acids, Acid anhydrides, Acid chlorides, Peroxides, Alkali metals

Hazardous Decomposition Products Carbon monoxide (CO), Carbon dioxide (CO_2)

Hazardous Polymerization Hazardous polymerization does not occur.

Hazardous Reactions None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information

Oral LD50 Based on ATE data, the classification criteria are not met. ATE > 2000 mg/kg.

Dermal LD50 Based on ATE data, the classification criteria are not met. ATE > 2000 mg/kg.

Vapor LC50 Based on ATE data, the classification criteria are not met. ATE > 20 mg/l.

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Ethyl alcohol	3450 mg/kg (Mouse)	Not listed	20000 ppm/10H (Rat)
Methyl alcohol	**Calc. ATE 60 mg/kg** LD50 > 1187 – 2769 mg/kg (Rat)	**Calc. ATE 60 mg/kg** LD50 = 17100 mg/kg (Rabbit)	**Calc. ATE 0.6 mg/L (vapours) or 0.5 mg/L (mists)** LC50 = 128.2 mg/L (Rat) 4 h

Methylisobutyl ketone	LD50 = 2080 mg/kg (Rat)	LD50 = 3000 mg/kg (Rabbit)	LC50 = 8.2 mg/L (Rat) 4 h
Ethyl acetate	10,200 mg/kg (Rat)	> 20 mL/kg (Rabbit) > 18000 mg/kg (Rabbit)	58 mg/l (rat; 8 h)
Hexane	LD50 = 25 g/kg (Rat)	LD50 = 3000 mg/kg (Rabbit)	LC50 = 48000 ppm (Rat) 4 h
Toluene	> 5000 mg/kg (Rat)	LD50 = 12000 mg/kg (Rabbit)	26700 ppm (Rat) 1 h
Ligroine	Not listed	Not listed	LC50 = 3400 ppm (Rat) 4 h

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation Severe eye irritant

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Ethyl alcohol	64-17-5	Group 1	Known	A3	X	Not listed
Methyl alcohol	67-56-1	Not listed	Not listed	Not listed	Not listed	Not listed
Methylisobutyl ketone	108-10-1	Group 2B	Not listed	A3	X	Not listed
Ethyl acetate	141-78-6	Not listed	Not listed	Not listed	Not listed	Not listed
Hexane	110-54-3	Not listed	Not listed	Not listed	Not listed	Not listed
Toluene	108-88-3	Not listed	Not listed	Not listed	Not listed	Not listed
Ligroine	8032-32-4	Not listed	Not listed	Not listed	Not listed	A3

IARC: (International Agency for Research on Cancer)
IARC: (International Agency for Research on Cancer)
Group 1 - Carcinogenic to Humans
Group 2A - Probably Carcinogenic to Humans
Group 2B - Possibly Carcinogenic to Humans

NTP: (National Toxicity Program)
NTP: (National Toxicity Program)
Known - Known Carcinogen
Reasonably Anticipated - Reasonably Anticipated to be a Human Carcinogen

ACGIH: (American Conference of Governmental Industrial Hygienists)
A1 - Known Human Carcinogen
A2 - Suspected Human Carcinogen
A3 - Animal Carcinogen
ACGIH: (American Conference of Governmental Industrial Hygienists)

Mexico - Occupational Exposure Limits - Carcinogens
Mexico - Occupational Exposure Limits - Carcinogens
A1 - Confirmed Human Carcinogen
A2 - Suspected Human Carcinogen
A3 - Confirmed Animal Carcinogen
A4 - Not Classifiable as a Human Carcinogen
A5 - Not Suspected as a Human Carcinogen

Mutagenic Effects Mutagenic effects have occurred in experimental animals.

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure Central nervous system (CNS) Optic nerve Respiratory system
STOT - repeated exposure Kidney Liver spleen Blood

Aspiration hazard No information available

Symptoms / effects,both acute and delayed Inhalation of high vapor concentrations may cause symptoms like headache, dizziness, tiredness, nausea and vomiting

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity

Contains a substance which is:. Toxic to aquatic organisms. The product contains following substances which are hazardous for the environment.

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Ethyl alcohol	EC50 (72h) = 275 mg/l (Chlorella vulgaris)	Fathead minnow (Pimephales promelas) LC50 = 14200 mg/l/96h	Photobacterium phosphoreum:EC50 = 34634 mg/L/30 min Photobacterium phosphoreum:EC50 = 35470 mg/L/5 min	EC50 = 9268 mg/L/48h EC50 = 10800 mg/L/24h
Methyl alcohol	Not listed	Pimephales promelas: LC50 > 10000 mg/L 96h	EC50 = 39000 mg/L 25 min EC50 = 40000 mg/L 15 min EC50 = 43000 mg/L 5 min	EC50 > 10000 mg/L 24h
Methylisobutyl ketone	EC50: 400 mg/L/96h	LC50: 496 - 514 mg/L, 96h flow-through (Pimephales promelas)	EC50 = 79.6 mg/L 5 min	EC50: 4280.0 mg/L/24h EC50: 170 mg/L/48h EC50: 4280.0 mg/L/24h
Ethyl acetate	EC50 = 3300 mg/L/48h	Fathead minnow: LC50: 230 mg/l/ 96h Gold orfe: LC50: 270 mg/L/48h	EC50 = 1180 mg/L 5 min EC50 = 1500 mg/L 15 min EC50 = 5870 mg/L 15 min EC50 = 7400 mg/L 2 h	EC50 = 717 mg/L/48h
Hexane	Not listed	LC50: 2.1 - 2.98 mg/L, 96h flow-through (Pimephales promelas)	Not listed	EC50: 3.87 mg/L/48h
Toluene	EC50: = 12.5 mg/L, 72h static (Pseudokirchneriella subcapitata) EC50: > 433 mg/L, 96h (Pseudokirchneriella subcapitata)	50-70 mg/L LC50 96 h 5-7 mg/L LC50 96 h 15-19 mg/L LC50 96 h 28 mg/L LC50 96 h 12 mg/L LC50 96 h	EC50 = 19.7 mg/L 30 min	EC50: = 11.5 mg/L, 48h (Daphnia magna) EC50: 5.46 - 9.83 mg/L, 48h Static (Daphnia magna)
Ligroine	EC50: = 4700 mg/L, 72h (Pseudokirchneriella subcapitata)	Not listed	Not listed	Not listed

Persistence and Degradability Persistence is unlikely based on information available.

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its volatility.

Component	log Pow
Ethyl alcohol	-0.32
Methyl alcohol	-0.74
Methylisobutyl ketone	1.19
Ethyl acetate	0.6
Hexane	4.11
Toluene	2.7

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

Component	RCRA - U Series Wastes	RCRA - P Series Wastes
Methyl alcohol - 67-56-1	U154	-
Methylisobutyl ketone - 108-10-1	U161	-

Ethyl acetate - 141-78-6	U112	-
Toluene - 108-88-3	U220	-

14. Transport information

DOT

UN-No	UN1170
Proper Shipping Name	ETHANOL
Hazard Class	3
Packing Group	II

TDG

UN-No	UN1170
Proper Shipping Name	ETHANOL
Hazard Class	3
Packing Group	II

IATA

UN-No	UN1170
Proper Shipping Name	ETHANOL
Hazard Class	3
Packing Group	II

IMDG/IMO

UN-No	UN1170
Proper Shipping Name	ETHANOL
Hazard Class	3
Packing Group	II

15. Regulatory information

All of the components in the product are on the following Inventory lists: Australia Complete Regulatory Information contained in following SDS's X = listed China Canada The product is classified and labeled according to EC directives or corresponding national laws The product is classified and labeled in accordance with Directive 1999/45/EC Europe TSCA Korea Philippines U.S.A. (TSCA) Canada (DSL/NDSL) Europe (EINECS/ELINCS/NLP) Australia (AICS) Korea (ECL) China (IECSC) Japan (ENCS) Philippines (PICCS)

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Ethyl alcohol	X	X	-	200-578-6	-		X	X	X	X	X
Methyl alcohol	X	X	-	200-659-6	-		X	X	X	X	X
Methylisobutyl ketone	X	X	-	203-550-1	-		X	X	X	X	X
Ethyl acetate	X	X	-	205-500-4	-		X	X	X	X	X
Hexane	X	X	-	203-777-6	438-390-3		X	X	X	X	X
Toluene	X	X	-	203-625-9	-		X	X	X	X	X
Ligroine	X	X	-	232-453-7	-		X	-	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313

Component	CAS-No	Weight %	SARA 313 - Threshold Values %
Methyl alcohol	67-56-1	<5	1.0
Methylisobutyl ketone	108-10-1	1.0 - 2.0	1.0
Hexane	110-54-3	<1	1.0
Toluene	108-88-3	<0.1	1.0

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act)

Component	CWA - Hazardous Substances	CWA - Reportable Quantities	CWA - Toxic Pollutants	CWA - Priority Pollutants
Toluene	X	1000 lb	X	X

Clean Air Act

Component	HAPS Data	Class 1 Ozone Depletors	Class 2 Ozone Depletors
Methyl alcohol	X		-
Methylisobutyl ketone	X		-
Hexane	X		-
Toluene	X		-

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA

Component	Hazardous Substances RQs	CERCLA EHS RQs
Methyl alcohol	5000 lb	-
Methylisobutyl ketone	5000 lb	-
Ethyl acetate	5000 lb	-
Hexane	5000 lb	-
Toluene	1000 lb 1 lb	-

California Proposition 65 Ethyl alcohol is only a considered a Proposition 65 developmental hazard when it is ingested as an alcoholic beverage This product contains the following proposition 65 chemicals

Component	CAS-No	California Prop. 65	Prop 65 NSRL	Category
Ethyl alcohol	64-17-5	Development (alcoholic beverages only)	-	Developmental Carcinogen
Methyl alcohol	67-56-1	Developmental	-	Developmental
Methylisobutyl ketone	108-10-1	Carcinogen Developmental	-	Developmental Carcinogen
Toluene	108-88-3	Developmental	-	Developmental

U.S. State Right-to-Know Regulations

Component	Massachusetts	New Jersey	Pennsylvania	Illinois	Rhode Island
Ethyl alcohol	X	X	X	X	X
Methyl alcohol	X	X	X	X	X
Methylisobutyl ketone	X	X	X	X	X
Ethyl acetate	X	X	X	-	X
Hexane	X	X	X	X	X
Toluene	X	X	X	X	X
Ligroine	-	X	X	-	-

U.S. Department of Transportation

Reportable Quantity (RQ):	N
DOT Marine Pollutant	N
DOT Severe Marine Pollutant	N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade Serious risk, Grade 3

16. Other information

Prepared By
Regulatory Affairs
Thermo Fisher Scientific
Email: EMSDS.RA@thermofisher.com

Creation Date 09-Jul-2009
Revision Date 18-Jan-2018
Print Date 18-Jan-2018
Revision Summary This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

ThermoFisher SCIENTIFIC

SAFETY DATA SHEET

Creation Date 02-Feb-2010 **Revision Date** 17-Jan-2018 **Revision Number** 4

1. Identification

Product Name Ethylene glycol

Cat No. : E177-4; E177-20

CAS-No 107-21-1
Synonyms Monoethylene glycol; 1,2-Ethanediol

Recommended Use Laboratory chemicals.
Uses advised against Not for food, drug, pesticide or biocidal product use

Details of the supplier of the safety data sheet

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Emergency Telephone Number
CHEMTREC®, Inside the USA: 800-424-9300
CHEMTREC®, Outside the USA: 001-703-527-3887

2. Hazard(s) identification

Classification
This chemical is considered hazardous by the 2012 OSHA Hazard Communication Standard (29 CFR 1910.1200)

Acute oral toxicity	Category 4
Specific target organ toxicity (single exposure)	Category 3
Target Organs - Central nervous system (CNS).	
Specific target organ toxicity - (repeated exposure)	Category 2
Target Organs - Kidney, Liver.	

Label Elements

Signal Word
Warning

Hazard Statements
Harmful if swallowed
May cause drowsiness or dizziness
May cause damage to organs through prolonged or repeated exposure

Precautionary Statements
Prevention
Wash face, hands and any exposed skin thoroughly after handling
Do not eat, drink or smoke when using this product
Do not breathe dust/fume/gas/mist/vapors/spray
Use only outdoors or in a well-ventilated area
Response
Get medical attention/advice if you feel unwell
Inhalation
IF INHALED: Remove victim to fresh air and keep at rest in a position comfortable for breathing
Call a POISON CENTER or doctor/physician if you feel unwell
Ingestion
IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell
Rinse mouth
Storage
Store in a well-ventilated place. Keep container tightly closed
Store locked up
Disposal
Dispose of contents/container to an approved waste disposal plant
Hazards not otherwise classified (HNOC)

WARNING. Reproductive Harm - https://www.p65warnings.ca.gov/.

3. Composition/Information on Ingredients

Component	CAS-No	Weight %
Ethylene glycol	107-21-1	>95

4. First-aid measures

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Get medical attention.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. Get medical attention immediately if symptoms occur.

Inhalation Move to fresh air. Do not use mouth-to-mouth method if victim ingested or inhaled the substance; give artificial respiration with the aid of a pocket mask equipped with a one-way valve or other proper respiratory medical device. Get medical attention immediately if symptoms occur. If not breathing, give artificial respiration.

Ingestion Do not induce vomiting. Call a physician or Poison Control Center immediately.

Most important symptoms and effects Breathing difficulties.

Notes to Physician Treat symptomatically

5. Fire-fighting measures

Suitable Extinguishing Media Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.

Unsuitable Extinguishing Media No information available

Flash Point 111 °C / 231.8 °F

Method - DIN 51758

Autoignition Temperature 413 °C / 775.4 °F

Explosion Limits
Upper 15.30 vol %
Lower 3.20 vol %
Sensitivity to Mechanical Impact No information available
Sensitivity to Static Discharge No information available

Specific Hazards Arising from the Chemical
Thermal decomposition can lead to release of irritating gases and vapors. Keep product and empty container away from heat and sources of ignition.

Hazardous Combustion Products
Carbon monoxide (CO) Carbon dioxide (CO_2)
Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA

Health	Flammability	Instability	Physical hazards
2	1	1	N/A

6. Accidental release measures

Personal Precautions Ensure adequate ventilation. Use personal protective equipment.
Environmental Precautions Should not be released into the environment. See Section 12 for additional ecological information.

Methods for Containment and Clean Up Soak up with inert absorbent material. Keep in suitable, closed containers for disposal.

7. Handling and storage

Handling Wear personal protective equipment. Ensure adequate ventilation. Do not breathe vapors or spray mist. Avoid contact with skin, eyes and clothing.

Storage Keep containers tightly closed in a dry, cool and well-ventilated place. Keep away from heat and sources of ignition.

8. Exposure controls / personal protection

Exposure Guidelines

Component	ACGIH TLV	OSHA PEL	NIOSH IDLH	Mexico OEL (TWA)
Ethylene glycol	TWA: 25 ppm STEL: 50 ppm STEL: 10 mg/m³	(Vacated) Ceiling: 50 ppm (Vacated) Ceiling: 125 mg/m³		Ceiling: 100 mg/m³

Legend

ACGIH *- American Conference of Governmental Industrial Hygienists*
OSHA *- Occupational Safety and Health Administration*

Engineering Measures Ensure adequate ventilation, especially in confined areas. Ensure that eyewash stations and safety showers are close to the workstation location.

Personal Protective Equipment

Eye/face Protection	Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.
Skin and body protection	Wear appropriate protective gloves and clothing to prevent skin exposure.
Respiratory Protection	Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.
Hygiene Measures	Handle in accordance with good industrial hygiene and safety practice.

9. Physical and chemical properties

Physical State	Viscous liquid Liquid
Appearance	Colorless
Odor	Odorless
Odor Threshold	No information available
pH	5.5-7.5 50% aq. sol
Melting Point/Range	-13 °C / 8.6 °F
Boiling Point/Range	196 - 198 °C / 384.8 - 388.4 °F @ 760 mmHg
Flash Point	111 °C / 231.8 °F
Method -	DIN 51758
Evaporation Rate	No information available
Flammability (solid,gas)	Not applicable
Flammability or explosive limits	
Upper	15.30 vol %
Lower	3.20 vol %
Vapor Pressure	0.12 mmHg @ 20 °C
Vapor Density	2.14 (Air = 1.0)
Specific Gravity	1.113
Solubility	miscible
Partition coefficient; n-octanol/water	No data available
Autoignition Temperature	413 °C / 775.4 °F
Decomposition Temperature	> 500°C
Viscosity	21 cP (20°C)
Molecular Formula	C2 H6 O2
Molecular Weight	62.06

10. Stability and reactivity

Reactive Hazard	None known, based on information available
Stability	Hygroscopic.
Conditions to Avoid	Incompatible products. Excess heat. Exposure to moist air or water.
Incompatible Materials	Strong oxidizing agents, Strong acids, Strong bases, Aldehydes
Hazardous Decomposition Products	Carbon monoxide (CO), Carbon dioxide (CO_2)
Hazardous Polymerization	Hazardous polymerization does not occur.
Hazardous Reactions	None under normal processing.

11. Toxicological information

Acute Toxicity

Product Information
Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
Ethylene glycol	7712 mg/kg (Rat)	9530 µL/kg (Rabbit) 10600 mg/kg (Rat)	Not listed

Toxicologically Synergistic Products No information available

Delayed and immediate effects as well as chronic effects from short and long-term exposure

Irritation May cause eye, skin, and respiratory tract irritation

Sensitization No information available

Carcinogenicity The table below indicates whether each agency has listed any ingredient as a carcinogen.

Component	CAS-No	IARC	NTP	ACGIH	OSHA	Mexico
Ethylene glycol	107-21-1	Not listed	Not listed	Not listed	Not listed	Not listed

Mutagenic Effects No information available

Reproductive Effects No information available.

Developmental Effects No information available.

Teratogenicity No information available.

STOT - single exposure Central nervous system (CNS)
STOT - repeated exposure Kidney Liver

Aspiration hazard No information available

Symptoms / effects,both acute and delayed No information available

Endocrine Disruptor Information No information available

Other Adverse Effects The toxicological properties have not been fully investigated.

12. Ecological information

Ecotoxicity
Do not empty into drains. .

Component	Freshwater Algae	Freshwater Fish	Microtox	Water Flea
Ethylene glycol	EC50: 6500 - 13000 mg/L, 96h (Pseudokirchneriella subcapitata)	LC50: = 16000 mg/L, 96h static (Poecilia reticulata) LC50: 40000 - 60000 mg/L, 96h static (Pimephales promelas) LC50: = 40761 mg/L, 96h static (Oncorhynchus mykiss) LC50: = 41000 mg/L, 96h (Oncorhynchus mykiss) LC50: 14 - 18 mL/L, 96h static (Oncorhynchus mykiss) LC50: = 27540 mg/L, 96h static (Lepomis macrochirus)	Not listed	EC50: = 46300 mg/L, 48h (Daphnia magna)

Persistence and Degradability Persistence is unlikely

Bioaccumulation/ Accumulation No information available.

Mobility Will likely be mobile in the environment due to its water solubility.

Component	log Pow
Ethylene glycol	-1.93

13. Disposal considerations

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

14. Transport information

DOT Not regulated
TDG Not regulated
IATA Not regulated
IMDG/IMO Not regulated

15. Regulatory information

All of the components in the product are on the following Inventory lists: X = listed

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	IECSC	KECL
Ethylene glycol	X	X	-	203-473-3	-		X	X	X	X	X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313

Component	CAS-No	Weight %	SARA 313 - Threshold Values %
Ethylene glycol	107-21-1	>95	1.0

SARA 311/312 Hazard Categories See section 2 for more information

CWA (Clean Water Act) Not applicable

Clean Air Act

Component	HAPS Data	Class 1 Ozone Depletors	Class 2 Ozone Depletors
Ethylene glycol	X		-

OSHA Occupational Safety and Health Administration
Not applicable

CERCLA This material, as supplied, contains one or more substances regulated as a hazardous substance under the Comprehensive Environmental Response Compensation and Liability Act (CERCLA) (40 CFR 302)

Component	Hazardous Substances RQs	CERCLA EHS RQs
Ethylene glycol	5000 lb	-

California Proposition 65 This product does not contain any Proposition 65 chemicals

Component	CAS-No	California Prop. 65	Prop 65 NSRL	Category
Ethylene glycol	107-21-1	Developmental	-	Developmental

U.S. State Right-to-Know Regulations

Component	Massachusetts	New Jersey	Pennsylvania	Illinois	Rhode Island
Ethylene glycol	X	X	X	X	-

U.S. Department of Transportation

Reportable Quantity (RQ): Y
DOT Marine Pollutant N
DOT Severe Marine Pollutant N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade Slight risk, Grade 1

16. Other information

Prepared By Regulatory Affairs
Thermo Fisher Scientific
Email: EMSDS.RA@thermofisher.com

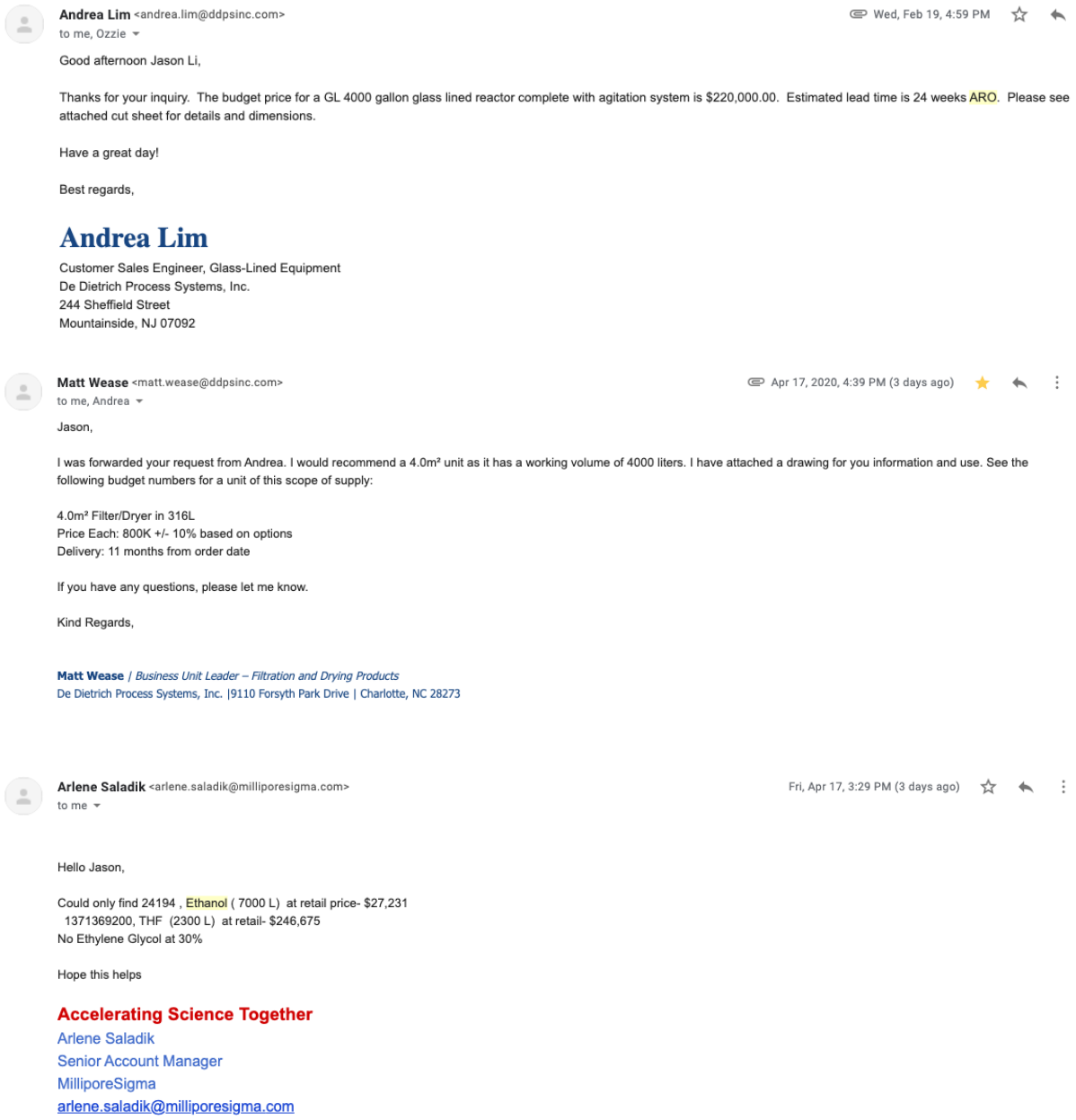
Creation Date 02-Feb-2010
Revision Date 17-Jan-2018
Print Date 17-Jan-2018
Revision Summary This document has been updated to comply with the US OSHA HazCom 2012 Standard replacing the current legislation under 29 CFR 1910.1200 to align with the Globally Harmonized System of Classification and Labeling of Chemicals (GHS).

Disclaimer
The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text

End of SDS

25.4 Detailed Specification Sheets

Emails of requests for quotes:



Andrea Lim <andrea.lim@ddpsinc.com> Wed, Feb 19, 4:59 PM
to me, Ozzie

Good afternoon Jason Li,

Thanks for your inquiry. The budget price for a GL 4000 gallon glass lined reactor complete with agitation system is $220,000.00. Estimated lead time is 24 weeks ARO. Please see attached cut sheet for details and dimensions.

Have a great day!

Best regards,

Andrea Lim
Customer Sales Engineer, Glass-Lined Equipment
De Dietrich Process Systems, Inc.
244 Sheffield Street
Mountainside, NJ 07092

Matt Wease <matt.wease@ddpsinc.com> Apr 17, 2020, 4:39 PM (3 days ago)
to me, Andrea

Jason,

I was forwarded your request from Andrea. I would recommend a 4.0m³ unit as it has a working volume of 4000 liters. I have attached a drawing for you information and use. See the following budget numbers for a unit of this scope of supply:

4.0m³ Filter/Dryer in 316L
Price Each: 800K +/- 10% based on options
Delivery: 11 months from order date

If you have any questions, please let me know.

Kind Regards,

Matt Wease | *Business Unit Leader – Filtration and Drying Products*
De Dietrich Process Systems, Inc. |9110 Forsyth Park Drive | Charlotte, NC 28273

Arlene Saladik <arlene.saladik@milliporesigma.com> Fri, Apr 17, 3:29 PM (3 days ago)
to me

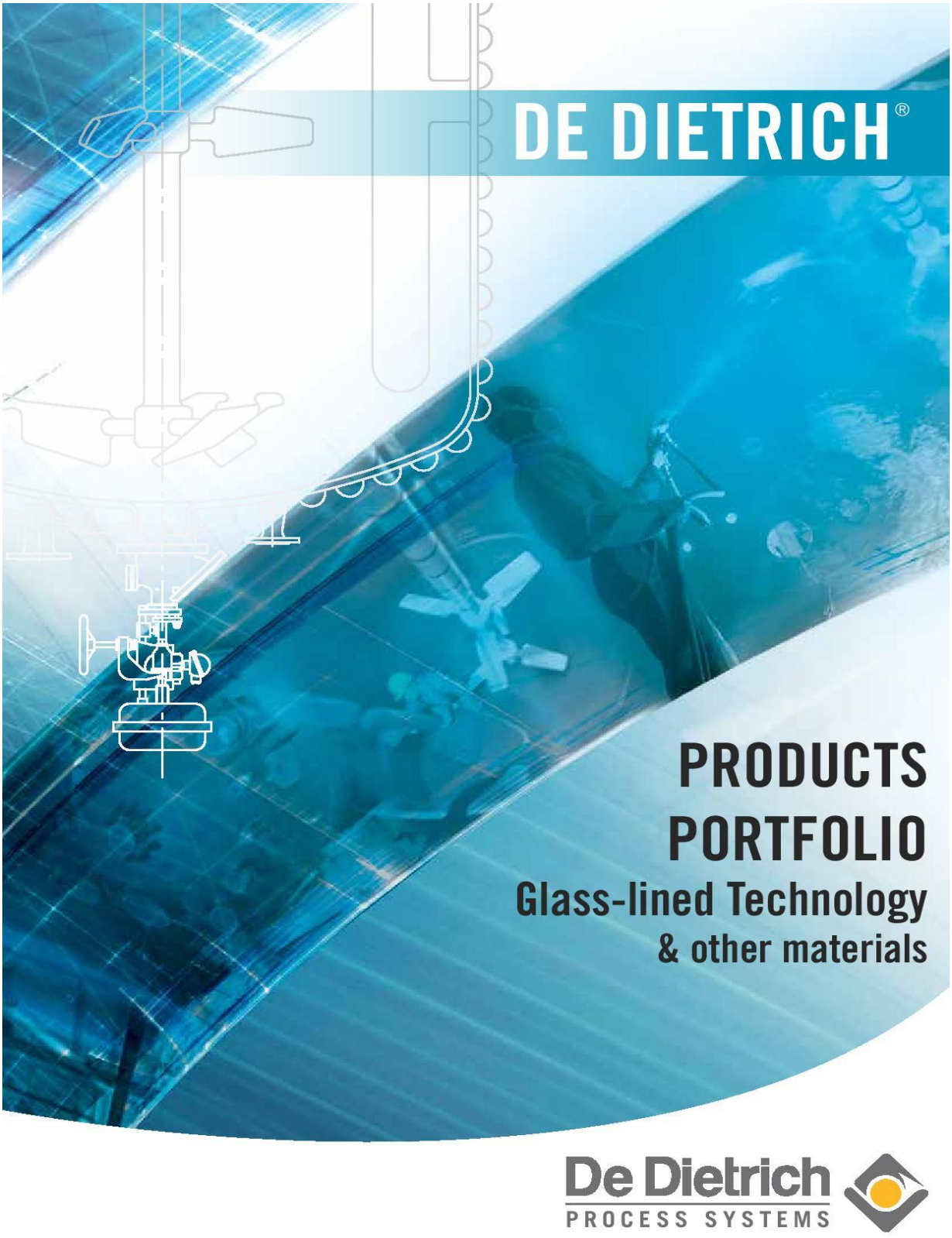
Hello Jason,

Could only find 24194 , Ethanol (7000 L) at retail price- $27,231
1371369200, THF (2300 L) at retail- $246,675
No Ethylene Glycol at 30%

Hope this helps

Accelerating Science Together
Arlene Saladik
Senior Account Manager
MilliporeSigma
arlene.saladik@milliporesigma.com

Reactor Vessel Specification Sheets:



De Dietrich

GENERAL INFORMATION

DE DIETRICH ENAMEL

REACTORS

MIXING TECHNOLOGY - GLASLOCK® SYSTEM

EQUIPMENT

BOTTOM OUTLET VALVE

PIPES & FITTINGS

INTRUMENTATION

CLEANABILITY

DE DIETRICH® HISTORY

The history of the de Dietrich family has been linked to that of France and of Europe for over three centuries. To this day, the company that bears the family name continues to play a major role in the economic life of Alsace.

De Dietrich® is one of the oldest manufacturing companies in France. It is located in the Vosges Mountains in North-Eastern France, where, as early as in the 17th century the rich natural resources of Alsace were beginning to be tapped.
The presence of iron-ore, forests and water power led to the building of blast-furnaces and forges.

In 1684, Jean Dietrich purchased the iron works of Jaegerthal.
His grandson Jean de Dietrich, ennobled by King Louis XV in 1761 for services rendered to the Crown, expanded the business by purchasing and enlarging the iron foundries and steel-mills of Zinswiller and around.

In 1778, King Louis XVI granted Jean de Dietrich the exclusive use of a trade mark (in the shape of an hunting horn) to protect his production from infringement.

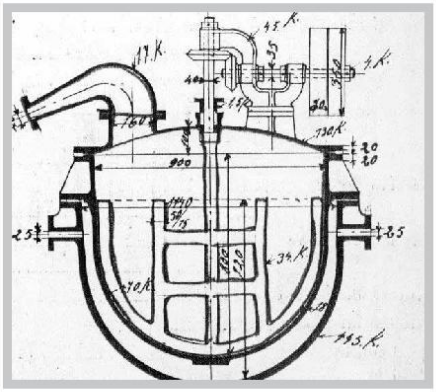
This symbol of quality is still the logo of the De Dietrich Group.

As early as in the middle of the 19th century, the Zinswiller plant was supplying all big chemical plants in Europe with glass-lined cast-iron reactors.

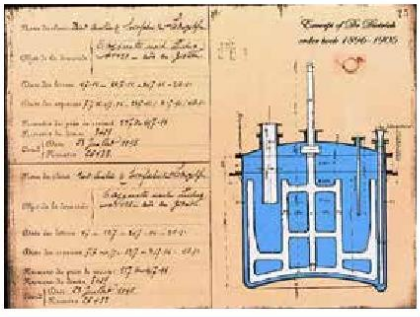
Ever since the development of this manufacturing technique has kept up with the great boom of the chemical industry.

The range of the products made in Zinswiller experienced a tremendous expansion and especially glass-lined steel replaced the initial cast-iron.

Thanks to its investments in labour force and equipment, De Dietrich® has never ceased to improve the quality of its products and especially that of enamels which has enabled the firm to retain a leading position in this particular field.



Distillation vessel of 150 l.
for the Strasbourg Exhibition in 1895



De Dietrich

THE COMPANY

De Dietrich© is the worldwide leader in the manufacture of glass-lined equipment, systems and accessories for the pharmaceutical and chemical industry.

The De Dietrich® competence center has expertise in:

- Glass-lined reactors
- Avanced Mixing Technology with OptiMix® design and GlasLock® system / Heat Transfer – Simulation capabilities
- Glass-lining technology
- Instrumentation
- Process solutions
- Engineered Systems
- Cleaning solutions (CIP)
- Range of solutions for Polyaluminium Chloride production units
- Powder transfer solutions: Powder Pump

Strongly based on our core activities:

- Our specialized and experienced process engineering teams are capable of developing conceptual studies and solutions to meet your requirements
- Feasibility studies and/or performance guarantees can be provided through our broad range of available technologies, process simulations and tests facilities
- We are a leading specialist for highly-corrosive media and high-pure materials
- Our technical expertise on the design and manufacture of key process equipment provides the optimum solution for specialty processes
- Our worldwide service, maintenance and support teams ensure your operations run efficiently

Our goal is to be your one stop shop for your complete processing needs.

De Dietrich

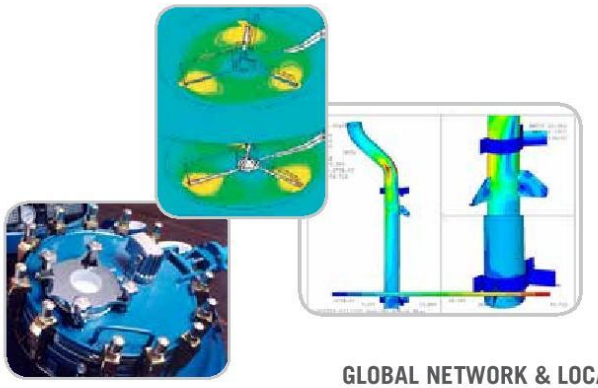
OUR SERVICES

SPARE PARTS
- Delivery to order, picking on shelf, shipment D+1
- Assembly to order
- Design & manufacturing to order
- Wide range of piping

FIELD SERVICE
- A team of technicians
- DDPS Network
- Commissioning
- Preventive Maintenance / Maintenance
- General Assistance

STOCK
- Equipment lifecycle management
- Optimized stock
- Spare parts list

REVAMPING / REGLASSING
- Refurbishment
- Process optimization
- Integration of all regulatory aspects



DESIGN
- Expertise in Codes and Legislations: DESP, ATEX, International Pressure Equipment
- Risks analysis
- EC Certification / U-Stamp
- Engineering - 3D - Simulations
- Optimized mixing technology
- Design of columns
- Heat transfer
- Finite element analysis

GLOBAL NETWORK & LOCAL EXPERTS

Phone: +33 3 (0)3 88 53 23 00
aftersales@dedietrich.com

Dear valued customer,

Aware that our customers from the chemical and pharmaceutical industries are global players who require suppliers capable of meeting their expectations on the world stage, De Dietrich Process Systems has been broadening its field of activity for a number of years and has developed its global presence to satisfy them and develop relations with the users of our products.
We now wish to be recognized in our markets as the leading supplier of the equipment, systems and services that we offer.

We are determined to develop customer satisfaction through irreproachable quality suited to growing needs, particularly in terms of performance, safety and pro-activeness in finding solutions suited to such needs. To achieve this, we involve the entire company at each level in the process.

Over and above the quality of our products and service provisions, industrial safety, health and working conditions, and respect for the environment must be present at all times in our day-to-day actions and taken into account as an essential factor to our development.

To achieve our ambition, we rely on:

- *Our company project*
- *Our know-how improved year on year in the specialized technologies which are glass lined steel, stainless steel and special alloys, mixing, instrumentation, the construction of equipment in borosilicate glass, and, more recently, our competence in process engineering and installing complete installations in materials resistant to corrosion, cleanable...*
- *Our integrated management system.*

As our products and service provisions are subject to the prevailing directives including, among others, the European Directives on Machinery, Pressure Equipment, Explosive Atmospheres, etc., quite some time ago we implemented manufacturing design, control and installation procedures in compliance with prevailing standards in the various countries where we have customers.

Our Service Center is available for any questions concerning our products and services.

Quality Management Direction

MECHANICAL PROPERTIES

Enamel is a glass with its qualities but also its main weaknesses which are brittleness and low tensile strength.
Since the resistance of glass to compression is well above its tensile strength, one of the solutions to improve the mechanical resistance is to put the glazed layer under compressive pre-stress. This is achieved during controlled cooling after each firing.
During mechanical work (deformation, mechanical or thermal shock) the compressive stress must first be offset by an equivalent tensile before the glass could be put under dangerous tensile stress.

ONE GLASS
WITH OPTIMUM QUALITY

DD3009, one glass with optimum quality for all products all over the world:

- Highly corrosive processes
- Abrasive product
- Multipurpose material / variety of uses
- Adapted to cGMP requirements, cleaning, cleanliness, sterilization
- Impervious: no catalytic effect, no contamination
- According to food contact (EC regulation n° 1935/2004)
- Anti-adhesive: polymerization processes

COLOR

- Blue (DD3009)
- White (DD3009 U)
- Light blue (DD3009 LB)
- Conductiglass (DD 3009 Conductiglass)

ABRASION

The abrasion test (ISO 6370-2: 2011) is far from the actual working conditions of a glass-lined reactor where the effects of the chemical attack enhance those of abrasion. Nevertheless, it allows a comparison between glasses, showing DD 3009 advantageously. Statistically, it has been shown that in practice the cases of destruction by abrasion are negligible. However, should any doubt arise when an abrasive substance is being used, only a comparative test performed with that product could lead to a conclusion.

MECHANICAL SHOCKS

The different experimental arrangements used for measuring the mechanical shock resistance produce results which cannot be compared to each other. Therefore, there is little use trying to give intrinsic values of the mechanical shock resistance. The only way to compare different glasses is to use the same method and the same criteria.

In our method, a 1 kg mass equipped with a 15 mm ball is dropped onto a glass-lined plate (glass thickness: 1.5 mm). This plate is locked onto a magnetic base, thereby making it thicker and increasing the shock efficiency (no energy absorption through steel vibrations). The plate is electrically grounded, and the electric current going through an electrolyte deposited at the shock location is used as assessment criteria. When tested to this procedure, which is close to the real service conditions, the mechanical shock resistance of the DD 3009 glass is about 80 % greater than that of the former glass.

THERMAL PROPERTIES

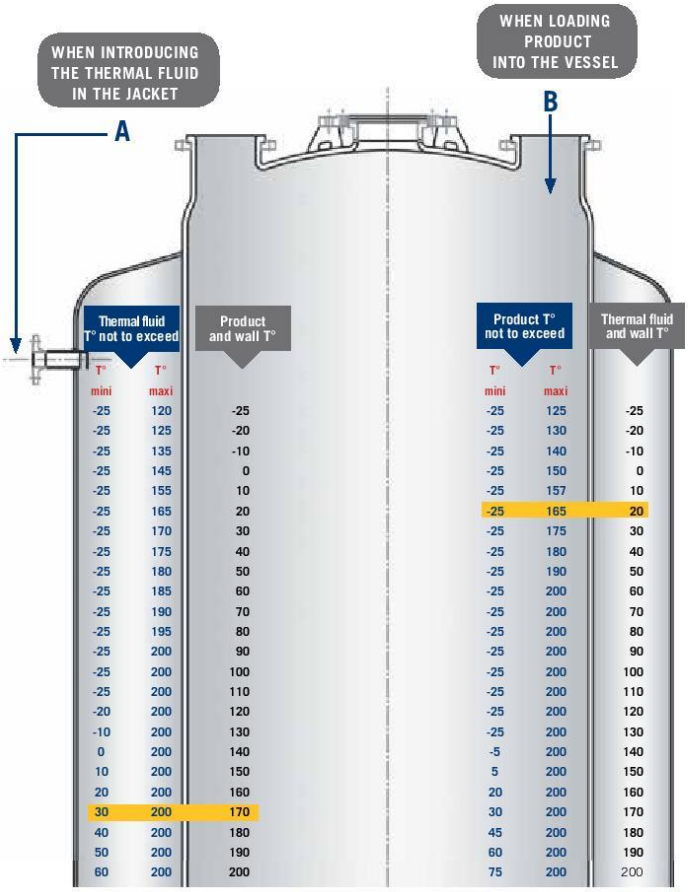
The large majority of equipment that we manufacture is designed with a system that enables the heating and cooling of their contents. As heat transfers may cause serious damage to the enamelled coating, the user should respect the limits described in this chapter, which take account both of the data in the ISO 28721-3: 2008 norm and our experience as a constructor of glass-lined equipment.

NOTE

Instructions devoted entirely to the thermal properties of the enamel are attached to the Maintenance Manual of our equipment and enamel leaflet to enable their installation and use in complete safety, as far as both your operators and the equipment are concerned.

HIGH THERMAL SHOCK RESISTANCE

GENERAL CASE OF STANDARD VESSELS CALCULATED FROM -25°C TO +200°C ISO 28721-3 NORM



Thermal fluid T° not to exceed		Product and wall T°
T° mini	T° maxi	
-25	120	-25
-25	125	-20
-25	135	-10
-25	145	0
-25	155	10
-25	165	20
-25	170	30
-25	175	40
-25	180	50
-25	185	60
-25	190	70
-25	195	80
-25	200	90
-25	200	100
-25	200	110
-20	200	120
-10	200	130
0	200	140
10	200	150
20	200	160
30	200	170
40	200	180
50	200	190
60	200	200

Product T° not to exceed		Thermal fluid and wall T°
T° mini	T° maxi	
-25	125	-25
-25	130	-20
-25	140	-10
-25	150	0
-25	157	10
-25	165	20
-25	175	30
-25	180	40
-25	190	50
-25	200	60
-25	200	70
-25	200	80
-25	200	90
-25	200	100
-25	200	110
-25	200	120
-25	200	130
-5	200	140
5	200	150
20	200	160
30	200	170
45	200	180
60	200	190
75	200	200

Example A
If the product and the glass-lined wall are at 170°C, the fluid temperature should be between +30°C and +200°C.

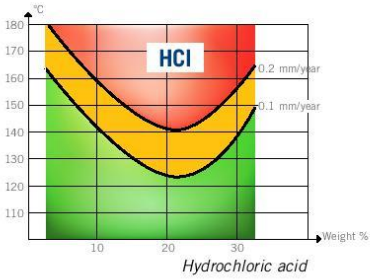
Example B
If the glass-lined wall and the thermal fluid are at 20°C, products between -25°C and +165°C may be safely introduced.

CHEMICAL PROPERTIES

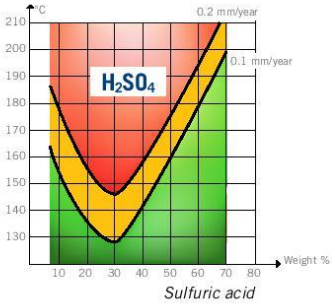
RESISTANCE TO ACIDS

Generally, DD 3009 glass has a high degree of resistance to acids whatever their concentration, up to relatively high temperatures. For most of the inorganic acids, the resistance of the glass passes through a minimum for a concentration of 20-30% weight, then increases with the acid concentration. For example, the 0.1 mm/year rate is found at 128°C in H_2SO_4 30% and at 180°C in H_2SO_4 60%. Exceptionally, in the case of phosphoric acid, the speed of attack increases with the concentration: 0.1 mm/year at 163°C for 10% concentration and at 112°C for 70% concentration.

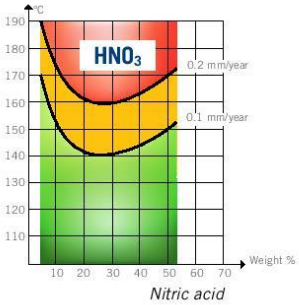
Hydrofluoric acid completely and quickly dissolves the glass whatever the temperature is. Its concentration in the product must not exceed 0.002% (20 ppm).



Hydrochloric acid



Sulfuric acid



Nitric acid

ISOCORROSION CURVES

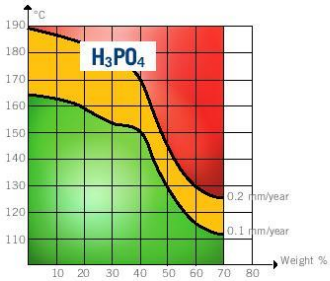
OUR ISOCORROSION CURVES ARE ESTABLISHED FOR MOST CURRENT PRODUCTS. THEY SHOW AS A FUNCTION OF PRODUCT CONCENTRATION THE TEMPERATURES AT WHICH THE WEIGHT LOSSES CORRESPOND TO 0.1 AND 0.2 MM/YEAR.

THE USE OF GLASS IS NOT ADVISABLE

CARE MUST BE TAKEN OF THE ADVANCE OF THE CORROSION

GLASS CAN BE USED WITHOUT PROBLEMS

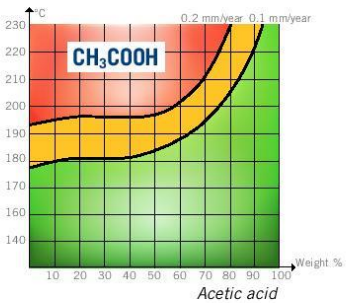
ALL THE TEST HAVE BEEN PERFORMED IN TANTALUM LINED REACTORS AND USING A RATIO VOLUME OF PRODUCT / SURFACE OF ENAMEL (V/S) > 20 TO AVOID THE INHIBITION OF THE ATTACK BY DISSOLVED SILICA.



Phosphoric acid

RESISTANCE TO ORGANIC SUBSTANCES

Chemical attack is very low in organic substances. If water is given off during the reaction, the rate of attack will depend on the amount of water in the solution. In the case of 0.1N sodium hydroxide in anhydrous alcohol at 80°C, the rate of attack is virtually nil. In methanol, there has to be more than 10% water before the loss of weight can be measured, whereas in ethanol with 5% water, the weight loss is already half of what it is in aqueous solution.

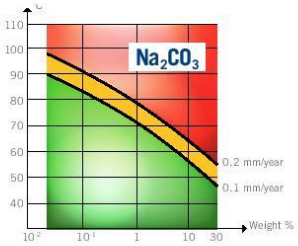


Acetic acid

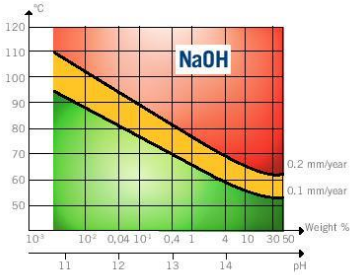
RESISTANCE TO ALKALIS

Here the permissible temperature limits are lower than for acids. At pH = 13 (NaOH 0.1N) this maximum is 70°C. Therefore, it is important to be cautious when using hot alkalis. Temperature must be controlled, as an increase of 10°C doubles the rate of attack of the glass. Care must be taken for the introduction of alkalis into a vessel. Avoid the flow of alkalis along the warm vessel wall by using a dip pipe.

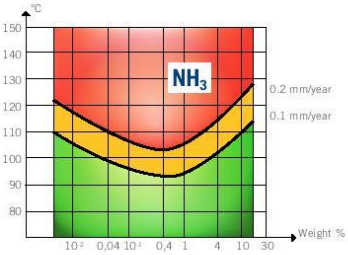
Corrosion values	Reference norm	Units	DD 3009 Glass
HCl 20% – Vapor 108°C	ISO 28706-2: 2008	mm/year	0.036
HCl 20 % - 140 °C – V/S = 20	ISO 28706-2: 2008	mm/year	0.2
NaOH 1N 80 °C – V/S = 20	ISO 28706-4: 2008	mm/year	0.35
NaOH 0.1 N 80 °C – V/S = 20	ISO 28706-4: 2008	mm/year	0.18
H_2O – Vapor	ISO 28706-2: 2008	mm/year	0.017
Thermal shocks – Statiflux surface cracks	ISO 13807: 1999	°C	220
Abrasion	ISO 6370-2: 2011	mg/cm²/h	2.35
Mechanical shocks	Improvement against former glass: 80 %		



Sodium carbonate



Sodium hydroxide



Ammonium hydroxide

RESISTANCE TO WATER VAPOR

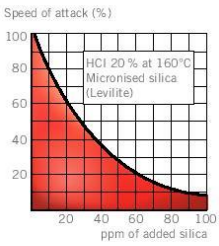
Resistance to water is excellent. The behavior of glass in neutral solutions depends on each individual case but in general is very satisfactory.

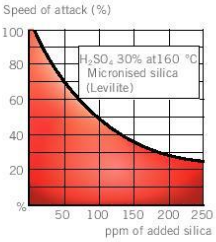
CORROSION INHIBITION

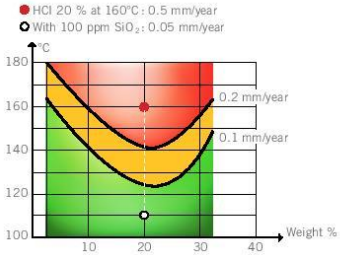
Chemical reactions are sometimes so severe they cause a rapid wear on the enamel surface. The use of additives to the reacting substance can inhibit this corrosion permitting the use of glass-lined equipment. When using acids, several tens or several hundreds ppm of silica protect the enamel and considerably reduce the rate of corrosion during the liquid phase.

The same result can be obtained at the vapor stage by adding silicon oils. Generally speaking, the higher the temperature, the greater the quantity of silica required, and more the acid is concentrated, the more the amount of silica can be reduced. In presence of fluorine, silica also has a favorable influence. We always recommend a pre-test as each reaction is different. An attack inhibitor can be useful in one case and yet non-effective in another.

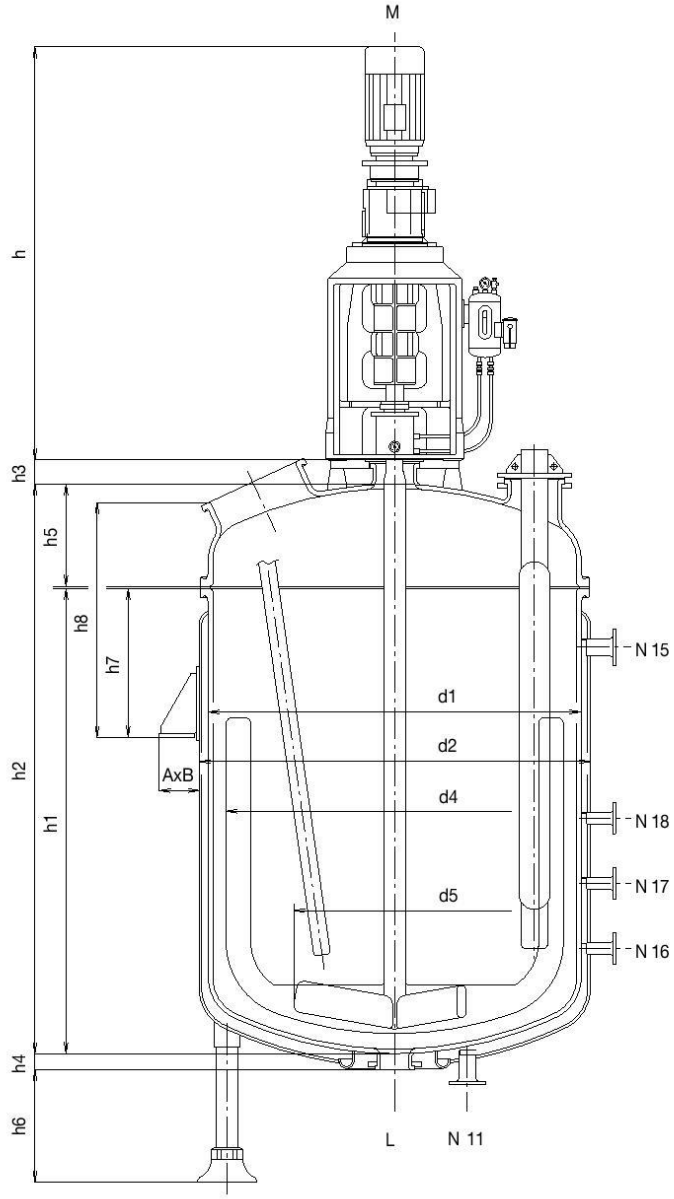
Corrosion values	Pure Product	500 ppm $CaCO_3$	300 ppm SiO_2	Silicon Oil 2 ml/l
NaOH 1N 80 °C	0.18 mm/year	0.09 mm/year		
Buffer pH= 1 ; 100°C + HF 430 ppm	1.5 mm/year		0.42 mm/year	
HCl 20 % vapor 110 °C	0.036 mm/year			< 0.005 mm/year

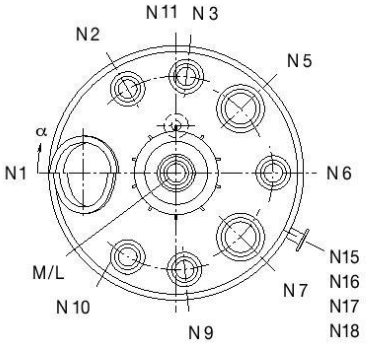


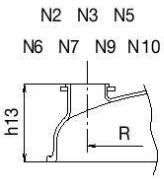


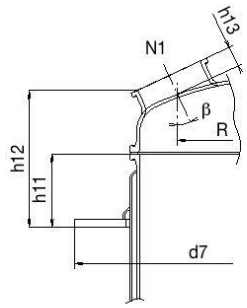


REACTORS









	Design pressure	Design temperature
Inside	-1/+6 bar	-25/+200° C
Jacket	-1/+6 bar	-25/+200° C
Half Coil	-1/+30 bar	-25/+235° C

	Allocation of Nozzles	
	Anchor	**Impeller**
N1	Manhole with sight glass	
N5 or N7	Thermowell	
N6	Light glass	
N2/N3/N9/N10	Free	

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			AE 1000	AE 1600	AE 2500	AE 4000	AE 6300
Nominal capacity		Litres	1000	1600	2500	4000	6300
Total capacity		Litres	1447	2309	3464	5374	8203
Jacket capacity		Litres	216	288	368	499	677
Heating area (with jacket)		m²	4,6	6,3	8,3	11,7	15,6
Approx. weight without motor and supporting		daN	2230	3240	4150	6000	8070
Main dimensions		d1	1200	1400	1600	1800	2000
		h1	1200	1400	1600	2000	2500
		d2	1300	1500	1700	1900	2100
		d4	1060	1250	1440	1630	1810
		d5	720	840	960	1100	1100
		h2	1550	1810	2070	2510	3060
		h3	100	100	100	130	130
		h4	75	70	70	70	85
		h5	340	400	460	500	550
Support System	Support legs	Quantity h6 min.	4 500	4 500	4 500	4 500	4 700
	Support lugs	A x B h7 min. h8 min.	160 x 160 405 710	180 x 220 475 830	180 x 220 485 885	200 x 320 630 1055	200 x 320 640 1105
	Support ring	d7 h11 min. h12 min.	1670 325 630	1890 345 700	2090 345 745	2290 370 795	2510 375 840
Nozzles on Vessel	M	DN	125	150	150	200	200
	L		100	100	100	100	150
	N1	DN / h13 R / β	350x450/125 440 / 25°	350x450/125 500 / 25°	350x450/125 580 / 25°	500 / 150 630 / 25°	500 / 700 700 / 25°
	N2	DN / h13 R / α	100 / 380 500 / 67,5°	100 / 425 575 / 60°	100 / 470 675 / 65°	150 / 500 725 / 65°	150 / 550 800 / 60°
	N3		100 / 380 500 / 95°	100 / 425 575 / 95°	100 / 470 675 / 95°	150 / 500 725 / 95°	150 / 550 800 / 95°
	N5		200 / 410 450 / 137,5°	200 / 450 550 / 135°	200 / 510 625 / 135°	250 / 525 675 / 135°	250 / 575 750 / 135°
	N6		100 / 380 500 / 180°	100 / 425 575 / 180°	100 / 470 675 / 180°	150 / 500 725 / 180°	150 / 550 800 / 180°
	N7		200 / 410 450 / 222,5°	200 / 450 550 / 225°	200 / 510 625 / 225°	250 / 525 675 / 225°	250 / 575 750 / 225°
	N9		100 / 380 500 / 265°	100 / 425 575 / 265°	100 / 470 675 / 265°	150 / 500 725 / 265°	150 / 550 800 / 265°
	N10		100 / 380 500 / 292,5°	100 / 425 575 / 300°	100 / 470 675 / 295°	150 / 500 725 / 295°	150 / 550 800 / 300°
Jacket Nozzles	N11	DN / α	50 / 90°	50 / 90°	50 / 90°	50 / 90°	80 / 90°
	N15		50 / 208°	50 / 208°	50 / 208°	50 / 208°	80 / 208°
	N16		50 / 208°	50 / 208°	50 / 208°	50 / 208°	50 / 208°
	N17		-	-	-	50 / 208°	50 / 208°
	N18		-	-	-	-	50 / 208°
Drive		MDL	60	80	80	100	100
		h *	1505	1940	1940	2155	2155

α : Orientation angle β : Tilt angle * with a standard motor

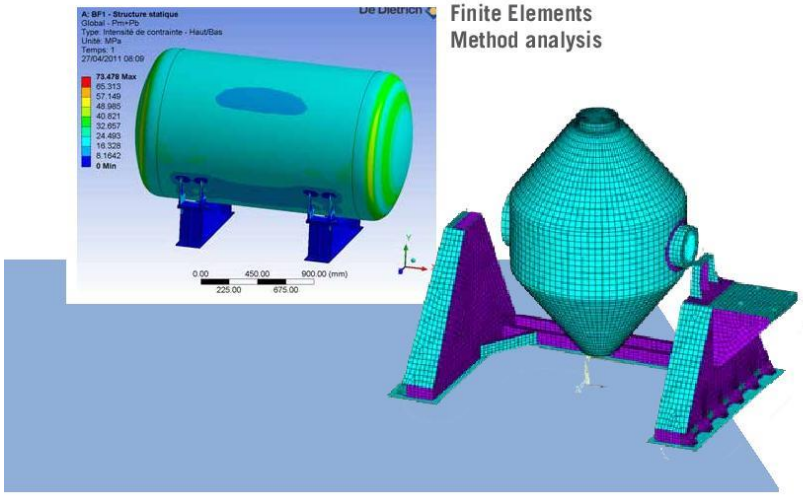
Reactor BE 80m³

Stripper 60m³
Eccentric agitation

4 reactors 110 m³
3 stages of
GlasLock® agitators

King size glass-lined reactor
Handling 75 tonnes

Wide range available up to 110m³ for glass-lined reactors and up to 140m³ for glass-lined tanks.



Finite Elements Method analysis

Sulfuric Acid Flash Evaporator 33.000 L

Elbow pipe DN1400

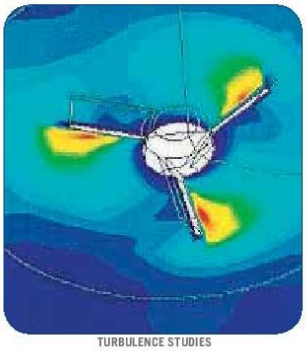
MIXING TECHNOLOGY - GLASLOCK® SYSTEM

COMPLETELY ADAPTABLE FOR YOUR PROCESS INTENSIFICATION

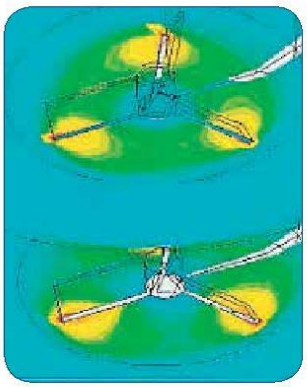
To improve process efficiency, De Dietrich® proposes a new experimental digital approach.

The programmes employed are various: pilot test stations with data acquisition in real time, study of flows generated by an agitator, establishment of the critical emulsion speed.

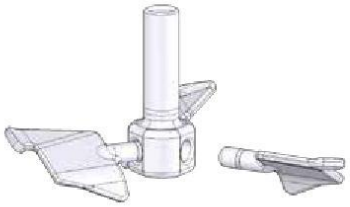
Digital simulation also finds an outlet in various applications: speed profile analysis around moving parts, primary run-off flows, turbulence studies, calculation of thermal data.

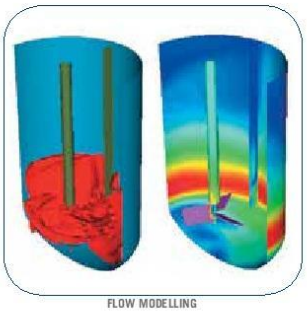


TURBULENCE STUDIES



SPEED PROFILE ANALYSIS AROUND MOVING PARTS





FLOW MODELLING

	GlasLock® system with removable blades									
	STANDARD PROFILES							NON STANDARD PROFILES		
Design	Flat Blade 30°	Flat Blade 45°	Flat Blade 60°	Flat Blade 90°	Trapezoidal Blade	Hydrofoil	Optifoil	ViscoFoil	Rushton Turbine	Breaker Bar
Reactor type	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX	AE-BE-CE OPX
Generated Flow	Axial	Axial Radial	Axial Radial	Radial	Axial Radial	Axial Radial	Axial Radial	Axial Radial	Radial	Axial Radial
Flow Model	Turbulent	Turbulent Laminar	Turbulent Laminar	Turbulent Laminar	Turbulent Laminar	Turbulent Laminar	Turbulent Laminar	Laminar	Turbulent	Turbulent Laminar
Tip Speed (m/s)	3 to 8	3 to 8	3 to 8	3 to 8	3 to 8	3 to 8	1 to 5	1 to 5	3 to 10	1 to 5
Viscosity Range (cP = mPa.s)	3 000	4 000	6 000	6 000	6 000	6 000	8 000	120 000	3 000	70 000
d / D	0,41 to 0,44	0,41 to 0,44	0,41 to 0,44	0,41 to 0,44	0,35 to 0,40	0,43 to 0,45	0,45 to 0,55	0,60 to 0,85	0,30 to 0,40	0,60 to 0,75
Homogenization	-	+	++	+	+	++	++	++	-	++
Suspension	-	+	++	++	++	++	+++	+	-	+
Dispersion	-	+	+	++	++	+	+	-	++	-
Gas / Liquid	-	-	+	+++	+++	-	-	-	+++	-
Heat Transfer	-	+	++	++	++	++	++	+++	+	++
Cristallization	++	++	+	-	-	++	+++	++	-	++

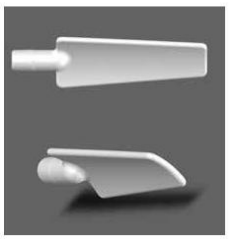
+ : suitable ++ : suit well +++ : suit perfectly - : not advisable

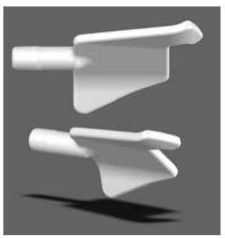
Reactor		Flat Blade					Trapezoidal				
Nominal Volume Litres	ø mm	Blade ø (mm)	Tail ø (mm)	Hub ø (mm)	Weight (kg)	Article Code	Blade ø (mm)	Tail ø (mm)	Hub ø (mm)	Weight (kg)	Article Code
1 000	1 200	660	58	190	8	7 614 486	660	58	190	8	7 617 042
1 600	1 400	660			8	7 614 486	660			8	7 617 042
2 500	1 600	750			10	7 614 487	750			11	7 617 024
4 000	1 800	750			10	7 614 487	750			11	7 617 024
6 300	2 000	850			13	7 614 488	850			13	7 617 031
8 000	2 200	850			13	7 614 488	850			13	7 617 031
10 000	2 400	1 050	70	222	21	7 614 489	1 050	70	222	23	7 617 061
12 500	2 400	1 050			21	7 614 489	1 050			23	7 617 061
16 000	2 600	1 050			21	7 614 489	1 050			23	7 617 061
20 000	2 800	1 200	88	270	33	7 614 490	1 200	88	270	30	7 617 087
25 000	3 000	1 200			33	7 614 490	1 200			30	7 617 087
32 000	3 400	1 372			38						
40 000	3 400	1 372			38						

Reactor		Hydrofoil					Optifoil				
Nominal Volume Litres	ø mm	Blade ø (mm)	Tail ø (mm)	Hub ø (mm)	Weight (kg)	Article Code	Blade ø (mm)	Tail ø (mm)	Hub ø (mm)	Weight (kg)	Article Code
1 000	1 200	720	58	190	7	7 614 444	740	58	190	10	7 617 083
1 600	1 400	720			7	7 614 444	740			10	7 617 083
2 500	1 600	850			9	7 614 445	900			14	7 617 078
4 000	1 800	850			9	7 614 445	950			14	7 617 082
6 300	2 000	950			14	7 614 446	1 050			21	7 617 077
8 000	2 200	950			14	7 614 446	1 050			21	7 617 077
10 000	2 400	1 100	70	222	18	7 614 447	1 300	70	222	38	7 617 080
12 500	2 400	1 100			18	7 614 447	1 300			38	7 617 080
16 000	2 600	1 200			20	7 614 448	1 300			38	7 617 080
20 000	2 800	1 350	88	270	30	7 614 449	1 450	88	270	43	7 617 072
25 000	3 000	1 350			30	7 614 449	1 450			43	7 617 072
32 000	3 400	1 450			38	7 617 039	1 600			46	7 617 084
40 000	3 400	1 450			38	7 617 039	1 600			46	7 617 084


Flat Blade


Trapezoidal Blade


Hydrofoil Blade


Optifoil Blade

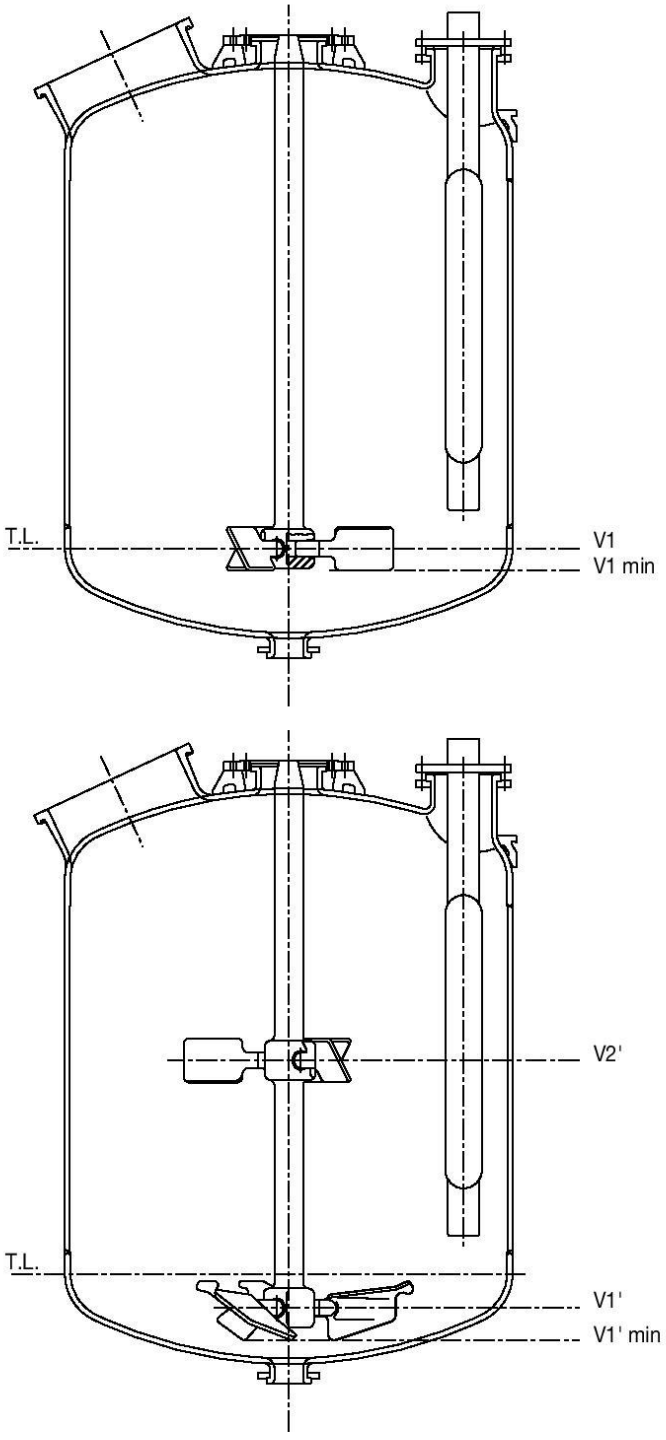


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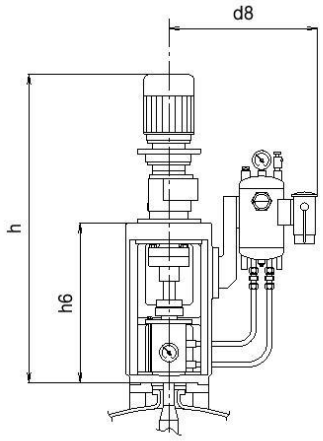
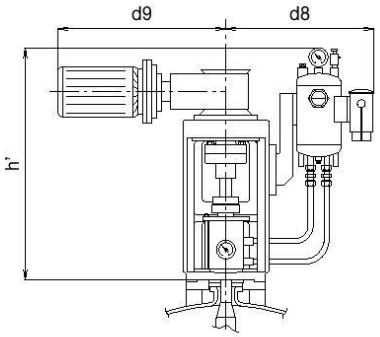
TABLE A STANDARD LENGTH		AGITATED VOLUMES	Minimum NON AGITATED VOLUMES (lower point of the lower blades)											
Reactor		(on blade axis)	Optifoil		Standard Flat Blade					Trapezoidal		Hydrofoil		
Nominal Volume Litres	ø mm	one level	Blade ø	V1 min	Blade ø	90° V1 min	60° V1 min	45° V1 min	30° V1 min	90° V1 min	60° V1 min	Blade ø	45° V1 min	
		V1												
1 000	1 200	158	740	56	660	75	85	98	115	48	61	720	70	
1 600	1 400	250	740	110	660	137	152	170	193	99	117	720	131	
2 500	1 600	330	900	129	750	165	183	203	289	140	168	850	215	
4 000	1 800	515	950	233	750	326	326	353	431	237	275	850	337	
6 300	2 000	705	1 050	283	850	441	448	525	586	332	383	950	485	
8 000	2 200	1 300	1 050	866	850	940	986	1 042	1 217	800	865	950	992	
10 000	2 400	1 690	1 300	922	1 050	1 143	1 220	1 304	1 414	906	1 005	1 100	1 255	
12 500	2 400	1 690	1 300	922	1 050	1 143	1 220	1 304	1 414	906	1 005	1 100	1 255	
16 000	2 600	2 140	1 300	1 241	1 050	1 638	1 593	1 692	1 822	1 222	1 340	1 200	1 510	
20 000	2 800	2 680	1 450	1 475	1 200	1 853	1 960	2 088	2 256	1 629	1 764	1 350	1 910	
25 000	3 000	3 300	1 450	1 905	1 200	2 342	2 465	2 613	2 806	2 082	2 238	1 350	2 407	
32 000	3 400	4 840	1 600	3 010	1 372	3 200	3 363	3 558	3 813	2 973	3 165	1 450	3 467	
40 000	3 400	4 840	1 600	3 010	1 372	3 200	3 363	3 558	3 813	2 973	3 165	1 450	3 467	

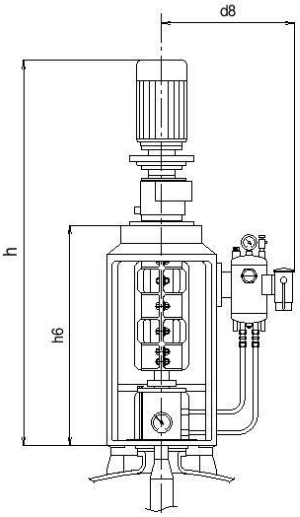
TABLE B EXTENDED LENGTH		AGITATED VOLUMES		Minimum NON AGITATED VOLUMES (lower point of the lower blades)										
Reactor		(on blade axis)		Optifoil		Standard Flat Blade					Trapezoidal		Hydrofoil	
Nominal Volume Litres	ø mm	1st level	2nd level	Blade ø	V1' min	Blade ø	90° V1' min	60° V1' min	45° V1' min	30° V1' min	90° V1' min	60° V1' min	Blade ø	45° V1' min
		V1'	V2'											
1 000	1 200	90	627	740	13	660	24	30	39	52	9	15	720	37
1 600	1 400	108	1 295	740	15	660	28	35	46	62	11	17	720	43
2 500	1 600	156	1 706	900	24	750	40	51	66	89	12	22	850	70
4 000	1 800	238	2 202	950	34	750	80	96	118	149	36	52	850	124
6 300	2 000	357	3 347	1 050	94	850	129	153	185	231	68	94	950	208
8 000	2 200	394	3 952	1 050	127	850	164	189	222	268	98	127	950	245
10 000	2 400	465	5 539	1 300	64	1 050	150	183	225	287	59	92	1 100	267
12 500	2 400	465	5 539	1 300	64	1 050	150	183	225	287	59	92	1 100	267
16 000	2 600	542	6 466	1 300	83	1 050	184	221	270	340	78	116	1 200	270
20 000	2 800	728	8 786	1 450	121	1 200	247	297	363	457	155	207	1 350	385
25 000	3 000	854	10 100	1 450	129	1 200	308	366	441	548	201	262	1 350	466
32 000	3 400	1 212	11 770	1 600	361	1 372	448	530	536	788	345	432	1 450	586
40 000	3 400	1 212	11 770	1 600	361	1 372	448	530	536	788	345	432	1 450	586



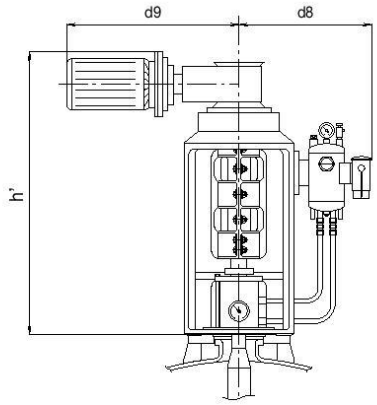
MDL 40-50



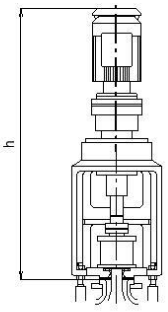
MDL 40-50



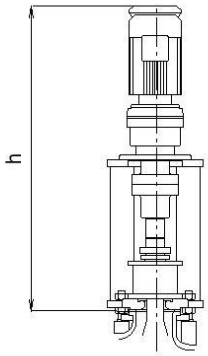
MDL 60-160



MDL 60-160



MNS 40-50



MNS 60-80

Reactor Type		MDL Type (Flange)	Constant Speed 50 Hz	Variable Speed 10-50Hz	High Variable Speed 10-60Hz	All types of standard agitators Impeller, GlasLock® Max. density / viscosity : 1300 kg/m3 / 500 cP (*)
			rpm			Motor Power (kW)
AE/OPX	63 100 160	40 (E125)	176	32/176	32/200	0,75
	250	50 (E200)	166	32/166		1,1
					32/184	1,5
	400	50 (E200)	166	32/166	32/184	1,5
AE/OPX/CE	630	60 (E250)	143	29/143		2,2
					29/166	3
AE	1000	60 (E250)	143	29/143		3
			169	29/169		4
BE/OPX	1000	80 (E300)	110	21/110	29/150	4
AE/BE/CE OPX	1600	80 (E300)	110	21/110		4
			111		21/125	5,5
	2500	80 (E300)	111	21/111		5,5
			114		21/125	7,5
CE	4000 AN	80 (E300)	114	30/114		7,5
					30/120	11
AE/BE/CE OPX	4000	100 (E400)	99	20/99		7,5
					20/115	11
	6300	100 (E500)	99	20/99		11
					20/115	15
BE/CE/OPX	8000	100 (E500)	99	20/99		11
					20/110	15
	10000 12500 16000	125 (E700)	79	25/79		18,5
			91		25/100	22
BE/CE	20000 25000	140 (E700)	73	20/73		30
			86		20/90	37
	32000 40000	160 (E900/1)	73	20/73		37
					20/90	45

Reactor Type		MDL Type (Flange)	Constant Speed 50 Hz	Variable Speed 10-50Hz	High Variable Speed 10-60Hz	Anchor agitator Max. density / viscosity: 1300 kg/m3 / 15 000 cP (*)
			rpm			Motor Power (kW)
AE	63 100 160	40 (E125)	112	21/112		0,75
	250	50 (E200)	79	15/79		1,1
					15/93	1,5
	400	50 (E200)	79	15/79	15/93	1,5 (max viscosity = 8 000 cP)
	630	60 (E250)	55	12/55		2,2
					12/65	3
	1000	60 (E250)	55	12/55		3
					12/65	4
	1600 2500	80 (E300)	38	8/38		4
			40		8/45	5,5
	4000	100 (E400)	30	6/30	6/36	7,5
	6300	100 (E500)	30	6/30		7,5
					6/36	11

(*) for higher values of viscosity or density, a simulation is required to calculate the necessary motor power

Agitator drive MDL	40	50		60			80				100			125		140		160**
Motor Power kW	0,75	1,1	1,5	2,2	3	4	4	5,5	7,5	11	7,5	11	15	18,5	22	30	37	45

h *	1040	1090	1115	1505	1505	1505	1725	1790	1825	1940	1995	2110	2155	2440	2475	2565	2680	3100
h' *	700	740	740	1105	1105	1105	1285	1305	1305	1335	1455	1480	1480	1720	1720	1770	1795	-
h6	510	535		865			1015				1150			1350		1350		1400
d8	470	515		510			580				690			770		770		600
d9 *	538	548	573	682	682	688	722	787	825	-	872	985	1030	1097	1135	1233	1347	-
Max. torque (Nm) **	50	150		320			800				1750			3200		5800		11800
Average Weight (daN) *	122	183		291			577				963			1519		1722		2600

Agitator drive MNS	40	50	60	80
Motor Power kW	1,1	2,2	4	5,5
h	1127	1238	1280	1511
Agitator speed (RPM)	121	120	113	92

* With a standard motor ** Depending on the reactor size

DRIVE UNIT
for glass-lined, stainless steel & alloy reactor

THE MAIN ADVANTAGES

- 3D modeling
- Flow modeling
- Turbulence studies
- Mixing simulation
- Improved heat exchange
- Optimization of the operating parameters
- Integration of all mechanical aspects
- Global certification: PED, ATEX, Machinery Directives, ...
- F.A.T. with dynamic test
- Easy maintenance by side dismantling of the mechanical seal

DE DIETRICH MECHANICAL SEAL

STANDARD DE DIETRICH - M06 VERSION

The De Dietrich mechanical seal M06 is a double liquid lubricated seal.
Atex: EX II 2 GD (either for Zone 1(Gas) or Zone 21 (Dust)).

The gas group IIA, IIB or IIC does not influence the seal selection.

Temperature classes:
- Basic RCRS version with oil lubrification is T3.
  For T4, choose the RSRS version

Combination of material:

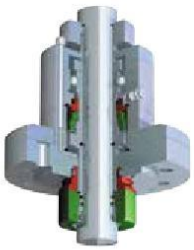
	RCRS (basic version)	RSRS	SSRS
Product side (PTFE wedge)	Carbon / Ceramic	Carbon / SIC	SIC / SIC
Atmospheric side (o-ring in FPM)	Carbon / SIC	Carbon / SIC	Carbon / SIC
Housing	Basic version: painted carbon steel - Also available with 316 stainless steel		

De Dietrich

CLEANABILITY

INTERNAL TECHNICAL SOLUTIONS

Inverted gas lubrificated mechanical seal
- Only C/SiC or SiC/SiC and enamel in contact with product
- Limited dead spots



Spraying devices
- A wide range of spraying devices (spray ball, spray ring) for an optimum cleanability
- Material: Alloy, PTFE, ...

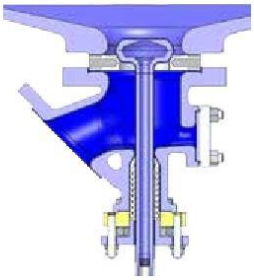
Block Flange

OptiMix®: optimization of the cleanability with 3 integrated baffles
- All the nozzles remain free for the process
- Better access for the cleaning
- No dead zones
- High axial flow behind the baffles to avoid deposit

EXTERNAL TECHNICAL SOLUTIONS

Welded insulation
- Foamglass or rockwool
- Welded stainless steel sheathing
- Complete insulation

CleanValve CVB with flat seat



Retractable spray device for outlet valve
- Directly installed on the side nozzle of the valve body
- No dismantling required for cleaning
- Conformity ATEX: CE II 2G IIC T4

Fused Glass
- No gaskets, no dead zones, easy cleaning
- Available as sight glass for nozzles
- Incorporated into Quick & Easy handhole cover
- Can be incorporated into flat cover
- Up from DN50 to DN200
  -1 / +10 bar

CIP SOLUTIONS (CLEANING IN PLACE)

Why investing in CIP: Cleaning In Place
- To save time to optimize your reactor operation
- To reduce solvent consumption for cleaning
- To define a repetitive cleaning cycle for constant efficiency

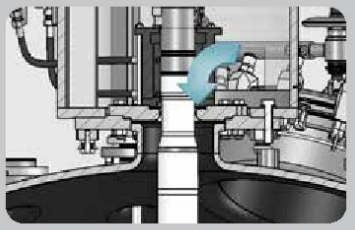
Our approach in 3 steps:
- Step 1: Cleaning specification sheet to understand your require
- Step 2: Optimized reactor design using results of cleaning study
- Step 3: Validation by test in our workshops or on your site

From a graphic study
- The user-oriented report highlights the potential areas non-accessible to the cleaning system, in order to optimize the reactor design and guide the choice towards the differents solutions.

In red, areas non-accessible for the spray ball

De Dietrich® designs the whole CIP System for your specific application

Mechanical seal with spraying system



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The international business group De Dietrich Process Systems is the leading provider of system solutions and reactors for corrosive applications as well as plants for mechanical solid/liquid separation and drying. The system solutions from De Dietrich Process Systems are used in the industrial areas of pharmaceuticals, chemicals and allied industries.

www.dedietrich.com

ADVANTAGE

- Hermetic production. No product is wasted and the risk of contamination is eliminated.
- Carrying out several operations using the same equipment: reaction / suspension, filtration, re-dissolution, washing and/or drying.
- Obtaining high purity and homogeneous products independently of the granulometry.
- Space and installation costs reduction.
- Full automatic and semi-automatic processes.
- Low energy consumption.
- Time reduction for cleaning, maintenance and filter element replacement.

FEATURES

- Filtering surface from 0.07 up to 15 m^2.
- Operation capacity from 19L up to 15.000L.
- Batch-wise operation.
- Design with absolute vacuum – Drying under vacuum and ultra vacuum.
- Design according to cGMP and EHEDG recommendations.
- Heating/ cooling of the body and/or agitator.
- Operating pressure of 3 bar(g)
- Operation Temperatures up to 200° C.
- Design according to ASME VIII div.1 – AD-2000 – EN-13445.

OPTIONS

- Internally mirror polished Ra ≤ 0.6 µm (Grit 360).
- Internally electro polished (Ra≤ 0.2 µm) as an option.
- External polishing according to requirements up to mirror polishing.
- CIP/SIP systems, validatable by Riboflavin test.
- Agitator with special sterile mechanical seal.
- Floating mechanical nitrogen seals.
- Drive unit with stainless steel cover.
- Sampling valve.
- Tight thermal insulation with welded stainless steel cover.
- Condensation system , vacuum and heating unit.
- Hardware and Software control.
- ATEX 20/0 execution with official certificate.
- DQ, IQ and OQ protocols.

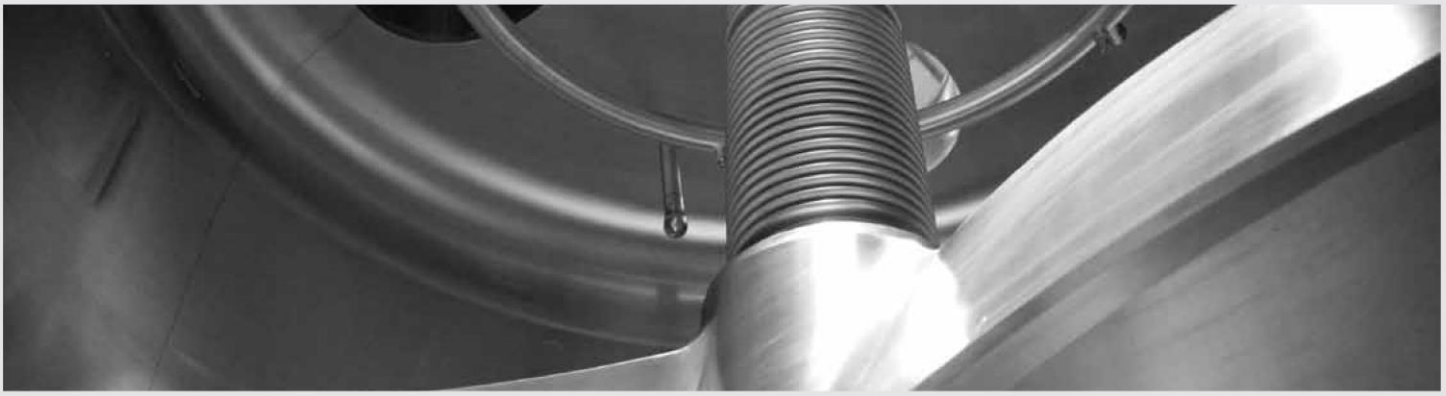
De Dietrich Process Systems Semur SAS

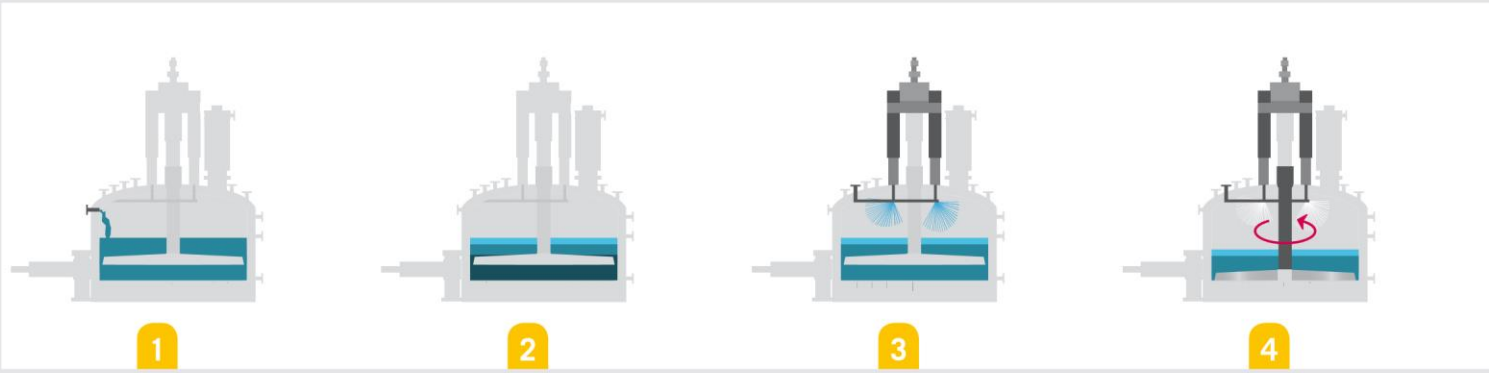
Nutsche filter dryer

De Dietrich
PROCESS SYSTEMS

Filter-dryer : Working principle

The Nutsche filter dryer combines two process operations, filtration and drying, in a single piece of equipment. Filtration (liquid-solid separation) and agitated vacuum drying allow batch manufacturing of chemical and pharmaceutical products. Filter dryers can also be used for other processes such as vegetal extraction.
Batch filtration-drying processes can be split in the following steps :





Filling | **Filtration** | **Piston displacement washing** | **Reslurry washing**

Turnkey Drying & Filtration units

Based on our extensive experience, **De Dietrich Process Systems** offer the complete engineering of your drying/filtration installation.

You have a single point of contact for your project, supplying a turnkey package integrating peripheral fonctions to the filter dryer :

- product transfert,
- containment,
- pressure control (vacuum skid),
- condensation,
- temperature control,
- skid building,
- etc...

1 Filling

The vessel is filled with a slurry (liquid/solid mixture), generally fed from a reactor or cristalliser

2 Filtration

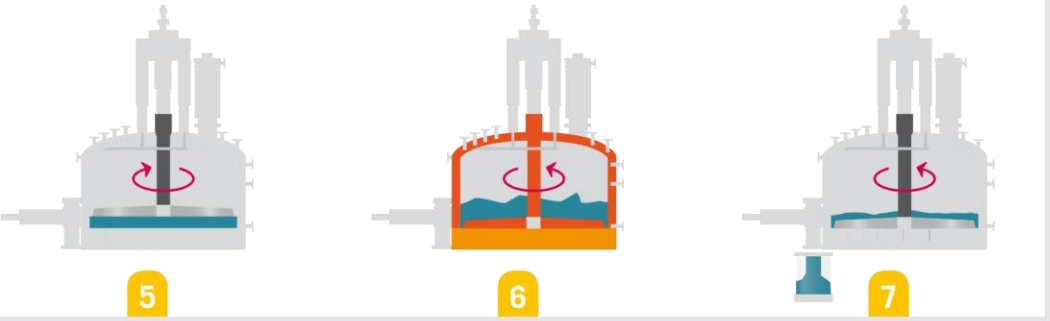
A liquid/solid separation process takes place through the filtration media. Filtrates (solvants) are collected beneath the filter plate

3 Piston displacement washing

Washing liquid are used to wash the product cake. A volume of liquid is displaced through the cake, washing it.

4 Reslurry washing

The agitator is used to re-slurry the solid in a washing solvent.



Smoothing | Drying and cooling | Discharging

5 Smoothing

The agitator (Guedu® or Rosenmund® shaped) is used to to smooth the wet cake in the filter dryer, to avoid the formation of cracks or preferential paths.

6 Drying and cooling

Agitated vacuum drying consists in applying a vacuum on the vessel, while heating the walls and agitator using thermal circuits. This allows to reach the liquid boiling point and to dry the product.

7 Discharging

The specially designed agitator pushes the product out towards a side discharge port.

Filtration

The flat base of the vessel is fitted with a filtration media, interchangeably be metallic or a textile cloth. machine, through a specially designed discharge valve or side opening.

- Efficient mixing for a good thermal homogeneity of the product during drying

De Dietrich + benefits

- GUEDU® Agitator design for improved mixing
- ROSENMUND® agitator profile for a simple, easily cleanable design

Drying

Drying is performed under vacuum, while agitating the product. A dust filter protects the vacuum source from potential contaminations. The heat input during drying is performed through the heated side walls, base and agitator. The dome and dust filter are maintained at a suitable temperature to avoid condensation.

De Dietrich + benefits

- Heated, 3-blade agitator providing over half the heat transfer during drying
- Dust filter with quick & easy maintenance
- On-line humidity measurement

De Dietrich + benefits

- Hygienic (GMP) design for pharmaceutical industries
- Interchangeability of different media types
- No hold up area between the filter media and base
- Quick lock of the filter base using a bayonet system

Discharging

The discharge is performed through the side of the that can be removable for ease of filter media change and glovebox. The agitator pushes the product out through the other maintenance operations.

Containment

De Dietrich offers containment solutions for filter-dryers, using soft-wall or rigid glovebox isolators, allowing operator protection during key operations such as discharge, sampling and dust filter change.

De Dietrich + benefits

- Metal/metal sealing, efficient even with abrasive or sticky materials
- Gas knife assisted discharge: nozzles located on an agitator arm are used to blow the product out using nitrogen. Up to 99% discharge efficiency
- Reverse seals with integrated dry or wet cleaning in place

Mixing and smoothing

The agitator design allows several successive operations :

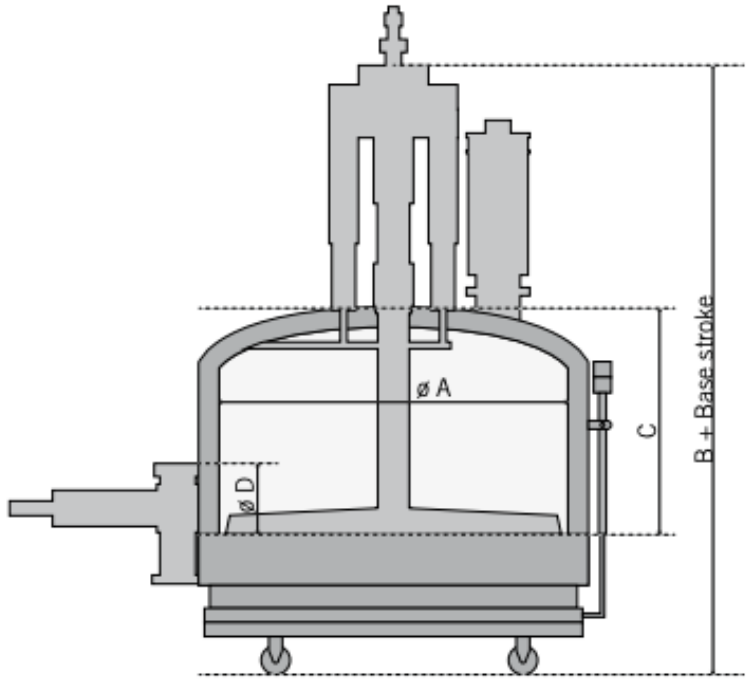
Controlling

The command of the various functions is performed through a PLC and operator interface panel. Various options are

- Smoothing of the cake at the end of filtration to avoid the available depending on the interface required. apparition of cracks or preferential paths

Trials / **Rentals solutions**

A number of small scale trial units are available for rental, for trials either at your site or in the DDPS Semur trial laboratory. In order to accurately size your equipment to satisfy your process requirement, drying and filtration trials can be performed with assistance of our process expert. He will assist you in performing the trials and provide you with a fully detailed report with recommendations on performance and successful scale-up.



Nutsche filter & filter dryer range

	Type RGFD / RGFR	Filtration surface (m²)	Agitator stroke (mm)	Base stroke (mm)	Cake volume (litres)	Usable volume ,litres)	Total volume (litres)	Ø A ext. (mm)	B (mm)	C (mm)	Ø D (mm)	Nominal drive power (kW)	Empty weight (kg)
Pilot range	0.03	0.03	200	15	6	17	24	203	1 981	640	70	0.75	330
	0.06	0.06	200	15	12	35	48	288	1 981	750	100	1.0	360
	0.1	0.1	250	15	30	80	100	400	1 981	960	150	1.35	420
	0.2	0.2	250	15	55	145	180	550	2 227	960	150	2.0	760
	0.3	0.3	250	15	75	185	230	630	2 227	960	200	2.5	860
	0.4	0.43	300	15	130	350	420	750	2 227	1 095	200	4.0/3.6	980
Production range	0.6	0.62	300	300	185	490	600	900	3 300	1 095	200	7.5/6.6	2 800
	1.0	1.11	400	300	440	1 050	1 310	1 200	3 300	1 335	400	11/8.5	3 200
	1.5	1.5	400	300	600	1 400	1 750	1 400	4 100	1 335	300	11/8.5	4 500
	2.0	1.97	400	400	800	1 800	2 260	1 600	4 100	1 335	300	11/8.5	5 500
	2.5	2.5	400	400	1 000	2 340	2 930	1 800	4 100	1 375	300	15/12	6 000
	3.0	3.09	400	400	1 200	2 860	3 580	2 000	4 300	1 375	300	18,5/15	6 500
	4.0	4.08	400	500	1 600	3 720	4 660	2 300	4 300	1 375	400	18,5/15	9 000
	5.0	4.83	500	500	2 400	5 220	6 530	2 500	4 600	1 600	400	22/18	12 000
	6.0	6.07	500	500	3 000	6 430	8 060	2 800	4 600	1 600	400	22/18	14 000
	8.0	7.94	500	Soudé	4 000	9 690	12 050	3 200	4 600	1 820	500	37/30	15 500
	10.0	10.63	500	Soudé	5 300	12 540	15 770	3 700	4 600	1 820	500	37/30	19 000

POWDER HANDLING SOLUTIONS

Powder Pump™

Description

The Powder Pump is a dense-phase pneumatic transfer system. It is designed to transfer a wide range of solids in a safe and contained manner. Simple in design, construction and operation, the Powder Pump enables solids charging into a vessel without the need to open a manway, thus maintaining the inert atmosphere inside the vessel. With proper solids analysis and testing, the Powder Pump can provide an ideal solution for transferring products of varying sizes and flow characteristics.

Applications

The Powder Pump is suitable for most processes in the chemical, pharmaceutical, food or flavor/fragrance industry where controlled, contained and efficient transfer of sensitive, hazardous or toxic solid materials is required.

Features

- Filter Sock rated for 99.9% efficiency @ 1-micron particle size
- Secondary port for spray ball or level-detection (see Image 1)
- Tool-less access to filter element to enable easy changeout (see Image 2)
- All components are anti-static/conductive and bonded for grounding

POWDER PUMP ADVANTAGES

- Closed system provides a dust-free environment
- Ability to charge with vessel under pressure, vacuum or with solvents already in vessel
- Ability to charge hazardous products
- Reduction/elimination of operator exposure or injury
- Wash-in-Place cleaning capability
- ASME and CRN code stamps available
- Minimal spare parts
- Reduces solids handling and eliminates hoists and handling equipment over the reactor

Want to see the Powder Pump in action? Visit www.ddpsinc.com/powderpump and watch our Powder Pump Demonstration Video online:

VISIT www.ddpsinc.com

CALL 908.317.2585

EMAIL sales@ddpsinc.com

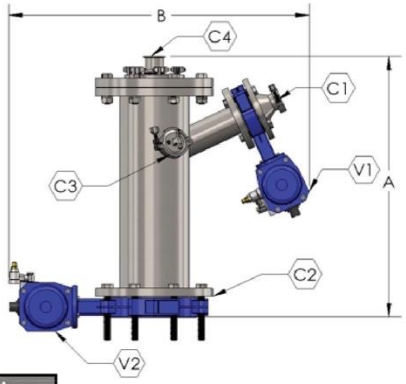
P002
1/2020

De Dietrich PROCESS SYSTEMS

Powder Pump™

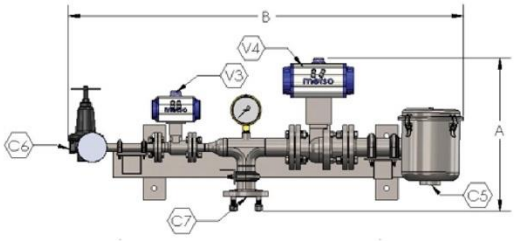
DIMENSIONAL AND UTILITY DATA*

- Sizes: 4", 6", 8" and 12"
- Available in 316 SS, Hastelloy or Glass
- Typical transfer distances are between 25-50 ft. Testing is highly recommended on anything beyond that distance.



	Valves		Connections			
Powder Pump	V1 Inlet Butterfly inches	V2 Outlet Butterfly inches	C1 Inlet Tri-clamp inches	C2 Outlet Flange inches	C3 2nd Port Tri-clamp inches	C4 Lid Tri-Clamp inches
PP-4	2	4	1.5	4	2.5	1.5
PP-6	2	6	1.5	6	2.5	1.5
PP-8	3	8	2	8	2.5	2
PP-12	3	12	2.5	12	2.5	3

	Approximate Weights					Approximate Dimensions	
Powder Pump	PP Body lbs	Outlet Valve lbs	Inlet Valve/ Adaptor lbs	Filter Access Cover lbs	Total lbs	A Overall Height inches	B Overall Width inches
PP-4	33.0	7.5	6.3	4.0	88.2	32.32	29.45
PP-6	46.8	15.1	6.3	4.0	124.4	32.32	29.76
PP-8	71.1	26.4	14.3	5.5	142.1	33.00	34.54
PP-12	126.0	54.7	14.3	27.3	287.7	37.20	42.50



	Valves		Connections		
Powder Pump	V3 Vacuum Ball inches	V4 Nitrogen Ball inches	C5 Filter NPT inches	C6 Regulator NPT inches	C7 Utility Hose Flange inches
PP-4	1.5	4	2	0.75	1.5
PP-6	1.5	6	2	0.75	1.5
PP-8	2	8	2	0.75	2
PP-12	3	12	3	1	3

	Approximate Weights				Approximate Dimensions	
Powder Pump	Mounting Bracket lbs	Valves lbs	Filter Housing lbs	Total lbs	A Overall Height inches	B Overall Width inches
PP-4	38.0	44.2	2.3	100.6	17.0	54.2
PP-6	38.0	44.2	2.3	100.6	17.0	54.2
PP-8	38.0	54.2	2.3	120.2	20.5	52.8
PP-12	49.5	91.4	40.3	219.5	23.4	72.0

*This data is for the standard Powder Pump, other configurations are available. Please contact DDPS to discuss your specific application and determine the system that is appropriate.

De Dietrich Process Systems, Inc.

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Mountainside, NJ 07092

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F 908.889.4960

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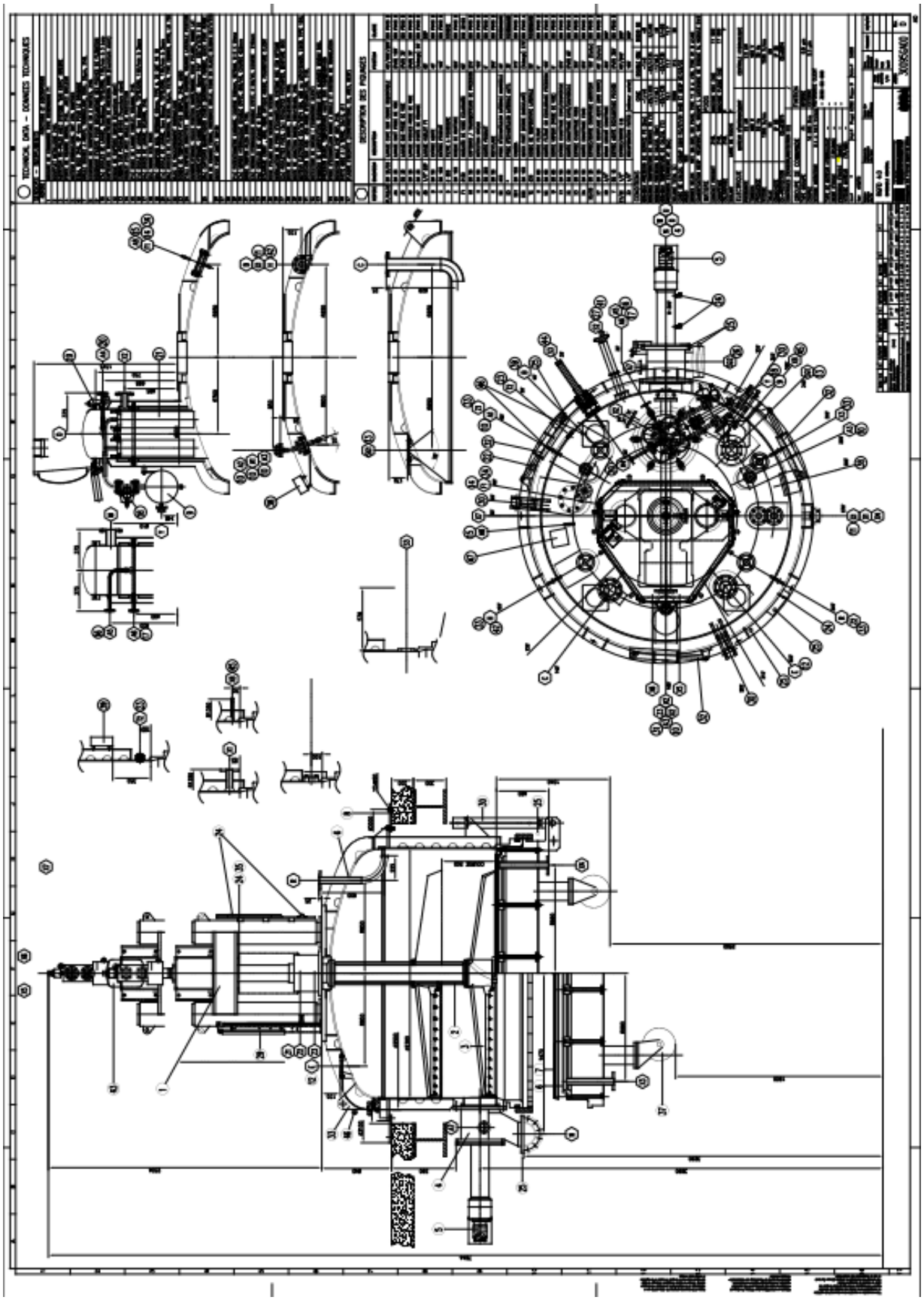
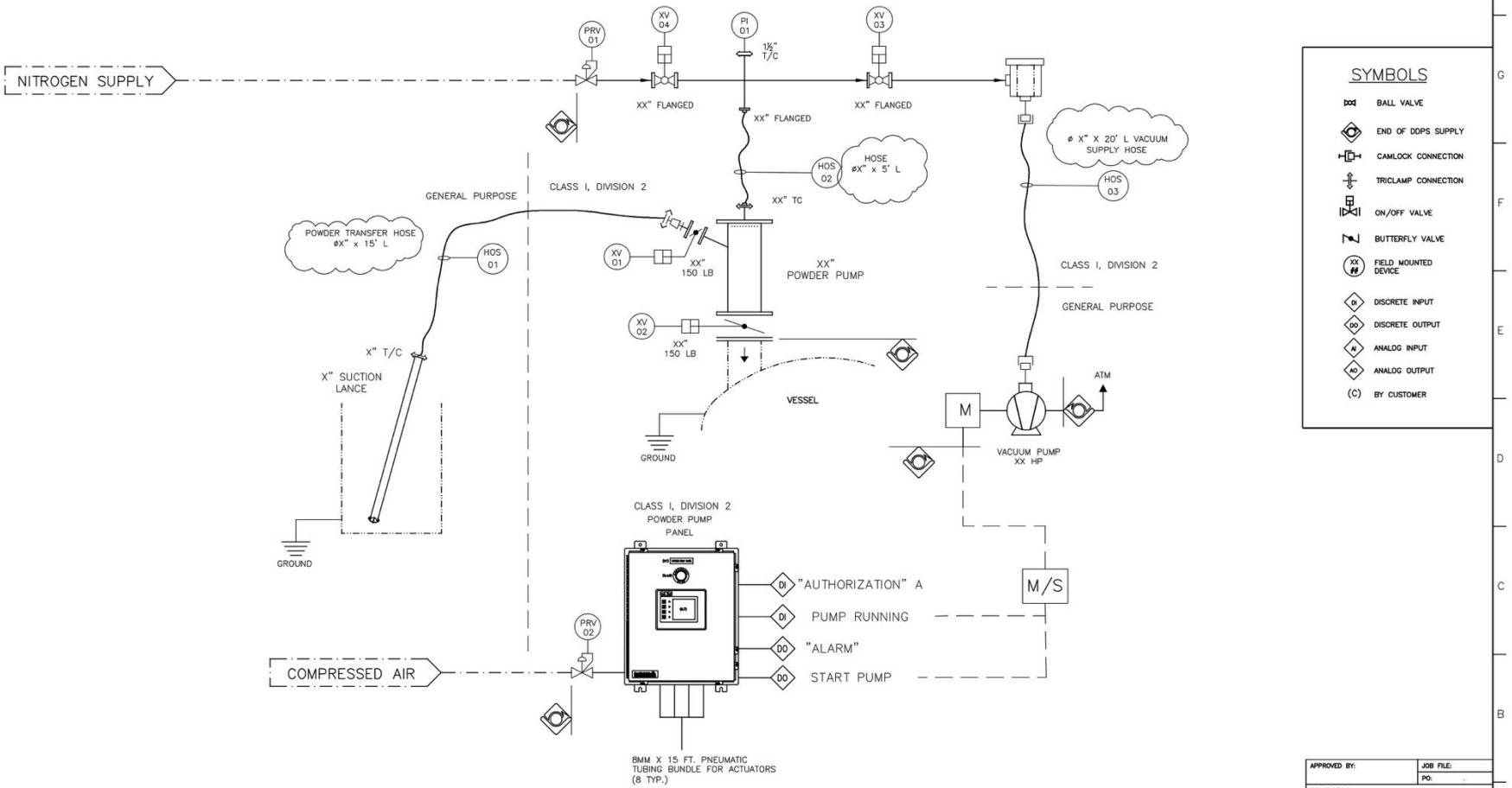
sales@ddpsinc.com

De Dietrich PROCESS SYSTEMS





MODEL	INLET BUTTERFLY VALVE (XV01)	OUTLET BUTTERFLY VALVE (XV02)	VACUUM BALL VALVE (XV03)	NITROGEN BALL VALVE (XV04)	TRANSFER HOSE ø (HOS 01)	UTILITY HOSE ø (HOS 02)	VACUUM HOSE ø (HOS 03)	VACUUM PUMP MOTOR	HP
PP-4	2" 150 LB. ANSI	4" 150 LB. ANSI	1.5" FLANGED	0.75" FLANGED	1.5"	1.5"	1.5"	R5-0100	5
PP-6	2" 150 LB. ANSI	6" 150 LB. ANSI	1.5" FLANGED	0.75" FLANGED	1.5"	1.5"	1.5"	R5-0205 OR R5-0255	7.5 OR 10
PP-8	3" 150 LB. ANSI	8" 150 LB. ANSI	1.5" FLANGED	0.75" FLANGED	2"	1.5"	1.5"	R5-0255 OR R5-0305	10 OR 12
PP-10	3" 150 LB. ANSI	10" 150 LB. ANSI	1.5" FLANGED	0.75" FLANGED	2"	1.5"	1.5"	R5-0305 OR R5-0400	12 OR 15
PP-12	3" 150 LB. ANSI	12" 150 LB. ANSI	2" FLANGED	1" FLANGED	2.5"	2"	2"	R5-0305 OR R5-0400	12 OR 15

APPROVED BY: | JOB FILE: | PO:

DESCRIPTION: POWDER PUMP PROCESS & INSTRUMENT DIAGRAM

De Dietrich PROCESS SYSTEMS

DRAWING # | REV. 0

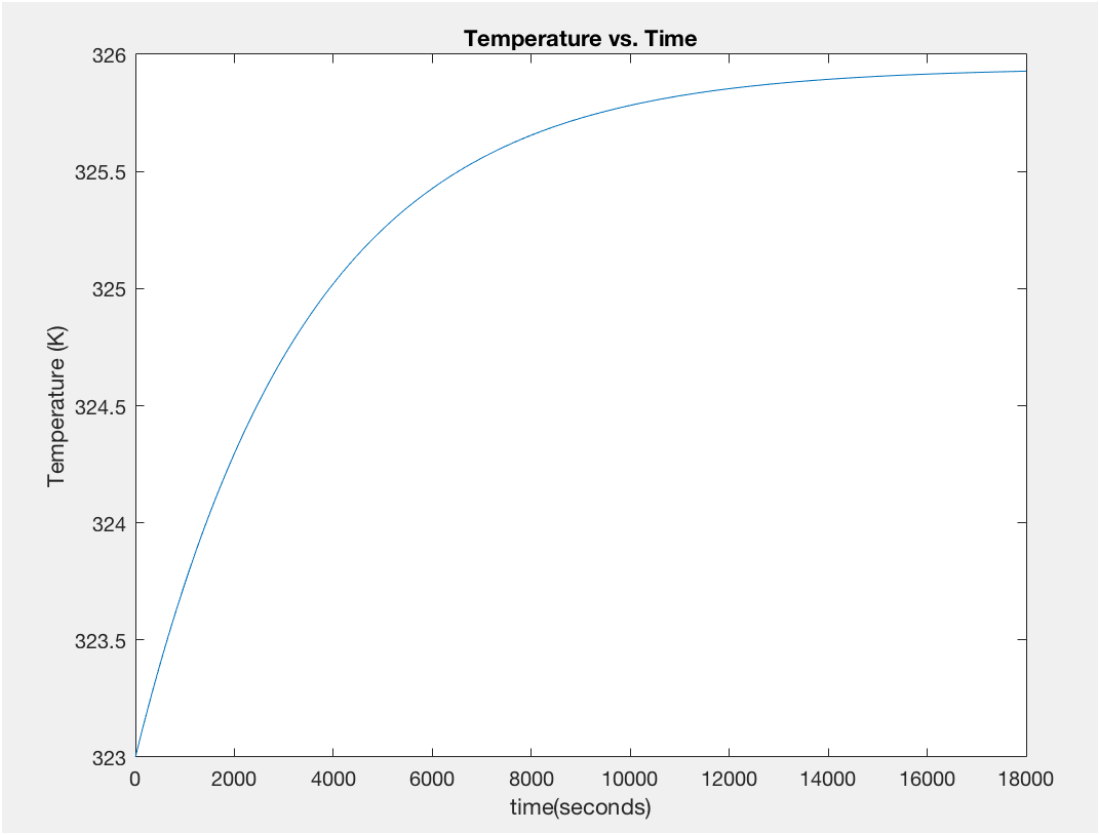
25.5 Aspen and Other Electronic Simulations

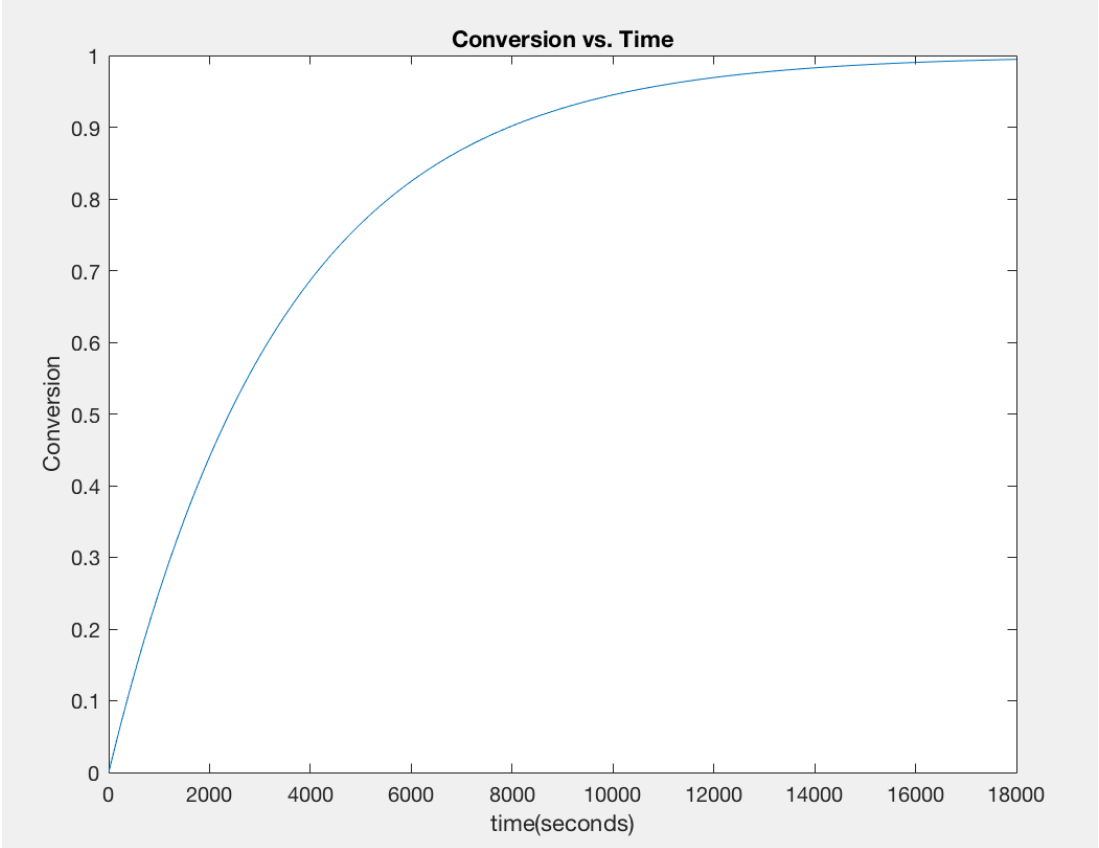
Reactor Plots of Conversion and Temperature as a Function of Time

$$\frac{dx}{dt} = Ae^{-\frac{E}{RT}}(1-x)$$

$$r \cdot C_p \cdot V_R \frac{dT}{dt} = \left\{-\Delta H_R \cdot Ae^{-\frac{E}{RT}} c_{Ao}(1-x) \cdot V_R + \dot{q}\right\}$$

```
clear all

tspan=0:30:18000;
init=[0;323]; %initial conditions of 50C at time zero
[t,y]=ode45(@fxn,tspan,init);
figure()
plot(t,y(:,2))
title('Temperature vs. Time')
xlabel('time(seconds)')
ylabel('Temperature (K)')
figure()
plot(t,y(:,1))
title('Conversion vs. Time')
xlabel('time(seconds)')
ylabel('Conversion')

function [dydt]=fxn(t,y)

A= 0.000291; %L mol/s
Hr = -27100; %J/mol
E= 8.95; %J/mol
Cp= 1.81; %J/g K
d= 889; %density g/L
cA0=0.1748; %mol/L
Vr=1300; %L
q=0;%for now
R=8.314; % J/mol-K
%k2=8.15e-3 ;

x=y(1);
T=y(2);

dydt=zeros(2,1);
dydt(1)=A*exp(-E/R/T)*(1-x);
dydt(2)=(-Hr*A*exp(-E/R/T)*(cA0)*(1-x)*Vr+q)/(d*Cp*Vr);
end
```


Temperature vs. Time
Temperature (K)
time(seconds)
326
325.5
325
324.5
324
323.5
323
0
2000
4000
6000
8000
10000
12000
14000
16000
18000


Conversion vs. Time
Conversion
time(seconds)
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2000
4000
6000
8000
10000
12000
14000
16000
18000

ASPEN Input and Results

The BATCHSEP block on ASPEN was used to model the solvent swap step. The model includes information about the vessel used in this process, AE-4000, and takes into account its exact dimensions. Based on iterative calculations as described in Section 25.2, the overall heat transfer coefficient was set to 330W/m^2-K, and the temperature of the jacket fluid was set to 102C. The block was initialized as being in total reflux initially, but the reflux ratio was immediately switched to 0 as the distillation began. The results from the simulation included the heat duty to both the vessel and the condenser, which were used to calculate the flow rate of the jacket fluid, as well as the flow rate and temperature of the steam and cooling water in the steam heat exchanger and the condenser, respectively. Although the steam reports are included, they are not indicative of the actual process because it is a batch process, not continuous.

ASPEN Input

```
;
;Input Summary created by Aspen Plus Rel. 37.0 at 22:01:20 Tue Apr 14, 2020
;Directory \\nestor\jinwanc\AspenTech\Aspen Plus V11.0  Filename
C:\Users\jinwanc\AppData\Local\Temp\~ap8f8f.txt
;


DYNAMICS
    DYNAMICS RESULTS=ON

IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm

DEF-STREAMS CONVEN ALL

SIM-OPTIONS MASS-BAL-CHE=YES UTL-REQD=NO

DATABANKS 'APV110 PURE37' / 'APV110 AQUEOUS' / 'APV110 SOLIDS' &
         / 'APV110 INORGANIC' / 'APESV110 AP-EOS' /  &
        'NISTV110 NIST-TRC' / NOASPENPCD

PROP-SOURCES 'APV110 PURE37' / 'APV110 AQUEOUS' /  &
        'APV110 SOLIDS' / 'APV110 INORGANIC' / 'APESV110 AP-EOS' &
         / 'NISTV110 NIST-TRC'

COMPONENTS
    THF C4H8O-4 /
    ETHANOL C2H6O-2 /
    NITROGEN N2 /
    WATER H2O /
    ETHYLEGL C2H6O2
```

```
SOLVE
    RUN-MODE MODE=SIM

FLOWSHEET
    BLOCK B1 IN=ETOH FEED OUT=DISTILLA BOTTOMS

PROPERTIES UNIQUAC
    PROPERTIES PENG-ROB

PROP-DATA UNIQ-1
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    PROP-LIST UNIQ
    BPVAL THF ETHANOL -1.788900000 381.9893000 0.0 0.0  &
        28.40000000 78.40000000 0.0
    BPVAL ETHANOL THF 1.600600000 -442.9157000 0.0 0.0  &
        28.40000000 78.40000000 0.0
    BPVAL THF WATER .3109718000 -611.0578000 0.0 0.0  &
        63.41000000 100.0000000 0.0
    BPVAL WATER THF -.3878309000 236.1184000 0.0 0.0  &
        63.41000000 100.0000000 0.0
    BPVAL ETHANOL WATER 2.004600000 -728.9705000 0.0 0.0  &
        24.99000000 100.0000000 0.0
    BPVAL WATER ETHANOL -2.493600000 756.9477000 0.0 0.0  &
        24.99000000 100.0000000 0.0
    BPVAL THF ETHYLEGL .2204000000 -343.8067000 0.0 0.0  &
        40.00000000 102.6400000 0.0
    BPVAL ETHYLEGL THF -.2432000000 70.81910000 0.0 0.0  &
        40.00000000 102.6400000 0.0
    BPVAL ETHANOL ETHYLEGL -8.230800000 2632.925500 0.0 0.0  &
        50.00000000 190.0000000 0.0
```

```
    BPVAL ETHYLEGL ETHANOL 2.687600000 -959.5647000 0.0 0.0  &
        50.00000000 190.0000000 0.0
    BPVAL WATER ETHYLEGL -.6018000000 120.7787000 0.0 0.0  &
        30.40000000 196.7000000 0.0
    BPVAL ETHYLEGL WATER .6018000000 -18.67140000 0.0 0.0  &
        30.40000000 196.7000000 0.0

PROP-SET K KMX UNITS='Watt/m-K' SUBSTREAM=MIXED PHASE=L

PROP-SET MASSCP CPMX-M SUBSTREAM=MIXED

PROP-SET RHO MASSRHOM SUBSTREAM=MIXED

PROP-SET VISCOSIT MUMX SUBSTREAM=MIXED PHASE=L

STREAM ETOH
    SUBSTREAM MIXED TEMP=20. PRES=1. STDVOL-FLOW=3000. <l/hr>
    MOLE-FRAC ETHANOL 1.

STREAM FEED
    SUBSTREAM MIXED TEMP=50. PRES=1. VOLUME-FLOW=1300.
    MOLE-FRAC THF 1. / ETHANOL 0.

BLOCK B1 BATCHSEP
    PARAMETERS USER-BYPASS=YES MODEL="BatchSep"
    STRINGPARAM NAME="CONFIGURATION" VALUE= &
        "Batch distillation column"
    STRINGPARAM NAME="VALIDPHASES" VALUE="Vapor-Liquid"
    STRINGPARAM NAME="INITIALCOND" VALUE="Total reflux"
    INTPARAM NAME="NSTAGE" VALUE=2
    STRINGPARAM NAME="CONDENSER.CONDENSERTYPE" VALUE="Total"
    STRINGPARAM NAME="PRIMARYCHARGEFLOWBASIS" VALUE="Mole"
```

```
INTPARAM NAME="CALCPROPS" VALUE=1
VARIABLES NAME="POT.D" VALUE=1800. UOM="MM"
VARIABLES NAME="POT.L" VALUE=1300. UOM="MM"
STRINGPARAM NAME="POT.VESSELID" VALUE="De dietrich-ae-4000"
STRINGPARAM NAME="POT.VESSELDESCRIPTION" VALUE= &
    "De dietrich din reactor ae 4000"
STRINGPARAM NAME="PRESSUREHOLDUPS" VALUE="Fixed"
VARIABLES NAME="CONDENSER.P" VALUE=1. UOM="BAR"
INTPARAM NAME="NDISTRECV" VALUE=1
VARIABLES NAME="LIQUIDRECV" VALUE=1
STRINGPARAM NAME="DISTRECVSTREAM(1)" VALUE="Distilla"
INTPARAM NAME="CHARGESTAGE(ETOH)" VALUE=2
STRINGPARAM NAME="INITIALCHARGESPEC" VALUE="Total charge"
STRINGPARAM NAME="POT.HOLDUPBASIS" VALUE="Mole"
VARIABLES NAME="POT.MINITIAL" VALUE=28.323 UOM="KMOL"
STRINGPARAM NAME="POT.HEATTRANSFER.JACKETHEATOPT" VALUE= &
    "Specified medium temperature"
VARIABLES NAME="POT.HEATTRANSFER.TMEDHEATJACKET" VALUE=102.  &
    UOM="C"
STRINGPARAM NAME="POT.HEATTRANSFER.UOPTHEATJACKET" VALUE= &
    "Overall"
VARIABLES NAME="POT.HEATTRANSFER.UHEATJACKET" VALUE=380. UOM= &
    "WATT/SQM-K"
VARIABLES NAME="POT.HEATTRANSFER.LHIGHJACKET" VALUE=1750.000000  &
    UOM="MM"
VARIABLES NAME="POT.HEATTRANSFER.UENV" VALUE=6. UOM= &
    "WATT/SQM-K"
VARIABLES NAME="OPSTEPMODEL(STARTUP).DURATION" VALUE=5. UOM= &
    "MIN"
VARIABLES NAME="OPSTEPMODEL(CONTADD).DURATION" VALUE=14. UOM= &
    "HR"
STRINGPARAM NAME="OPSTEPS" VALUE= &
```

```
    "[STARTUP,ADDETOH1,CONTADD,DISTILLF]"
STRINGPARAM NAME="SUPPORTMULTIPLETRIGGERS" VALUE="Yes"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).VARS" VALUE="[1:3]"
INTPARAM NAME="OPSTEPSVALID(STARTUP)" VALUE=1
INTPARAM NAME="OPSTEPMODEL(STARTUP).ACTIVE" VALUE=1
INTPARAM NAME="OPSTEPMODEL(STARTUP).INDEX" VALUE=1
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(1).LOC" VALUE= &
    "Jacket"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(1).HTMODE" VALUE= &
    "Heating"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(1).CHANGE" VALUE= &
    "Medium temperature"
VARIABLES NAME="OPSTEPMODEL(STARTUP).CHANGE(1).NEWPOTTMED"  &
    VALUE=50. UOM="C"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(2).LOC" VALUE= &
    "Charge stream"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(2).CHARGE" VALUE= &
    "Etoh"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(2).CHANGE" VALUE= &
    "Mole flow rate"
VARIABLES NAME="OPSTEPMODEL(STARTUP).CHANGE(2).NEWMOLEFLOW"  &
    VALUE=0. UOM="KMOL/HR"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(3).LOC" VALUE= &
    "Reflux splitter"
STRINGPARAM NAME="OPSTEPMODEL(STARTUP).CHANGE(3).CHANGE" VALUE= &
    "Reflux ratio"
VARIABLES NAME="OPSTEPMODEL(STARTUP).CHANGE(3).NEWREFLUXRATIO"  &
    VALUE=0.
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).VARS" VALUE="[1:3]"
INTPARAM NAME="OPSTEPSVALID(ADDETOH1)" VALUE=1
INTPARAM NAME="OPSTEPMODEL(ADDETOH1).ACTIVE" VALUE=1
INTPARAM NAME="OPSTEPMODEL(ADDETOH1).INDEX" VALUE=2
```

```
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(1).LOC" VALUE= &
    "Charge stream"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(1).CHARGE" VALUE= &
    "Etoh"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(1).CHANGE" VALUE= &
    "Mole flow rate"
VARIABLES NAME="OPSTEPMODEL(ADDETOH1).CHANGE(1).NEWMOLEFLOW"  &
    VALUE=55. UOM="KMOL/HR"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(2).LOC" VALUE= &
    "Reflux splitter"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(2).CHANGE" VALUE= &
    "Reflux ratio"
VARIABLES NAME="OPSTEPMODEL(ADDETOH1).CHANGE(2).NEWREFLUXRATIO"  &
    VALUE=0.
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(3).LOC" VALUE= &
    "Jacket"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(3).HTMODE" VALUE= &
    "Heating"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).CHANGE(3).CHANGE" VALUE= &
    "Medium temperature"
VARIABLES NAME="OPSTEPMODEL(ADDETOH1).CHANGE(3).NEWPOTTMED"  &
    VALUE=102. UOM="C"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).VARS" VALUE="[1:3]"
INTPARAM NAME="OPSTEPSVALID(CONTADD)" VALUE=1
INTPARAM NAME="OPSTEPMODEL(CONTADD).ACTIVE" VALUE=1
INTPARAM NAME="OPSTEPMODEL(CONTADD).INDEX" VALUE=3
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(1).LOC" VALUE= &
    "Charge stream"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(1).CHARGE" VALUE= &
    "Etoh"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(1).CHANGE" VALUE= &
    "Mole flow rate"
```

```
VARIABLES NAME="OPSTEPMODEL(CONTADD).CHANGE(1).NEWMOLEFLOW"  &
    VALUE=8.9 UOM="KMOL/HR"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(2).LOC" VALUE= &
    "Reflux splitter"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(2).CHANGE" VALUE= &
    "Reflux ratio"
VARIABLES NAME="OPSTEPMODEL(CONTADD).CHANGE(2).NEWREFLUXRATIO"  &
    VALUE=0.
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(3).LOC" VALUE= &
    "Jacket"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(3).HTMODE" VALUE= &
    "Heating"
STRINGPARAM NAME="OPSTEPMODEL(CONTADD).CHANGE(3).CHANGE" VALUE= &
    "Medium temperature"
VARIABLES NAME="OPSTEPMODEL(CONTADD).CHANGE(3).NEWPOTTMED"  &
    VALUE=102. UOM="C"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).VARS" VALUE="[1:3]"
INTPARAM NAME="OPSTEPSVALID(DISTILLF)" VALUE=1
INTPARAM NAME="OPSTEPMODEL(DISTILLF).ACTIVE" VALUE=1
INTPARAM NAME="OPSTEPMODEL(DISTILLF).INDEX" VALUE=4
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(1).LOC" VALUE= &
    "Charge stream"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(1).CHARGE" VALUE= &
    "Etoh"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(1).CHANGE" VALUE= &
    "Mole flow rate"
VARIABLES NAME="OPSTEPMODEL(DISTILLF).CHANGE(1).NEWMOLEFLOW"  &
    VALUE=0. UOM="KMOL/HR"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(2).LOC" VALUE= &
    "Jacket"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(2).HTMODE" VALUE= &
    "Heating"
```

```
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(2).CHANGE" VALUE= &
    "Medium temperature"
VARIABLES NAME="OPSTEPMODEL(DISTILLF).CHANGE(2).NEWPOTTMED"  &
    VALUE=102. UOM="C"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(3).LOC" VALUE= &
    "Reflux splitter"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).CHANGE(3).CHANGE" VALUE= &
    "Reflux ratio"
VARIABLES NAME="OPSTEPMODEL(DISTILLF).CHANGE(3).NEWREFLUXRATIO"  &
    VALUE=0.
INTPARAM NAME="OPSTEPMODEL(ADDETOH1).NTRIGGER" VALUE=1
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).TRIGGERLOC(1)" VALUE= &
    "Pot"
STRINGPARAM NAME="OPSTEPMODEL(ADDETOH1).TRIGGER(1)" VALUE= &
    "Liquid volume"
VARIABLES NAME="OPSTEPMODEL(ADDETOH1).TRIGGERVOLUME(1)" VALUE= &
    4000. UOM="L"
INTPARAM NAME="OPSTEPMODEL(DISTILLF).NTRIGGER" VALUE=1
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).TRIGGERLOC(1)" VALUE= &
    "Pot"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).TRIGGER(1)" VALUE= &
    "Liquid volume"
STRINGPARAM NAME="OPSTEPMODEL(DISTILLF).TRIGGERCOND(1)" VALUE= &
    "Approach from above"
VARIABLES NAME="OPSTEPMODEL(DISTILLF).TRIGGERVOLUME(1)" VALUE= &
    2500. UOM="L"
STRINGPARAM NAME="POTFINALCOND" VALUE="Leave in place"
INTPARAM NAME="CALCPROPS" VALUE=1
INTPARAM NAME="HEATLOSS" VALUE=1
STRINGPARAM NAME="POT.MODELDETAIL" VALUE="Detailed"
INTPARAM NAME="POT.HEATTRANSFER.EXTHXHEATING" VALUE=0
INTPARAM NAME="POT.HEATTRANSFER.EXTHXCOOLING" VALUE=0
```

```
    INTPARAM NAME="POT.HEATTRANSFER.JACKETHEATING" VALUE=1
    INTPARAM NAME="POT.HEATTRANSFER.JACKETCOOLING" VALUE=0
    INTPARAM NAME="POT.HEATTRANSFER.COILSHEATING" VALUE=0
    INTPARAM NAME="POT.HEATTRANSFER.COILSCOOLING" VALUE=0
    CONNECT STREAM=BOTTOMS PORT="OUT_B"
    CONNECT STREAM=ETOH PORT="IN_F"
    CONNECT STREAM=FEED PORT="IN_CHARGE"
    CONNECT STREAM=DISTILLA PORT="OUT_D"

UTILITY U-1 GENERAL
    COST PRICE=0.00939 <$/lb>
    PARAM UTILITY-TYPE=GENERAL PRES=1. PRES-OUT=1. TIN=100.  &
        TOUT=90. CALOPT=FLASH
    COMPOSITION WATER 1.

EO-CONV-OPTI

STREAM-REPOR MOLEFLOW

PROPERTY-REP PCES

PROP-TABLE BINRY-1 FLASHCURVE
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    PROPERTIES UNIQUAC FREE-WATER=STEAM-TA SOLU-WATER=3  &
        TRUE-COMPS=YES
    MOLE-FLOW THF 1 /  ETHANOL  1
    STATE VFRAC=0.0
    ANALYSIS ANAL-TYPE=TXY
    VARY PRES
    RANGE LIST=0.1
    VARY MOLEFRAC COMP=THF
```

```
    RANGE VARVALUE=RANGE LOWER=0.0 UPPER=1.0 NPOINT=50
    PARAM NPHASE=3

PROP-TABLE BINRY-2 FLASHCURVE
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    PROPERTIES UNIQUAC FREE-WATER=STEAM-TA SOLU-WATER=3  &
        TRUE-COMPS=YES
    MOLE-FLOW THF 1 /  ETHANOL  1
    STATE VFRAC=0.0
    ANALYSIS ANAL-TYPE=TXY
    VARY PRES
    RANGE LIST=0.1
    VARY MOLEFRAC COMP=THF
    RANGE VARVALUE=RANGE LOWER=0.0 UPPER=1.0 NPOINT=50
    PARAM NPHASE=3

PROP-TABLE BINRY-3 FLASHCURVE
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    PROPERTIES UNIQUAC FREE-WATER=STEAM-TA SOLU-WATER=3  &
        TRUE-COMPS=YES
    MOLE-FLOW THF 1 /  ETHANOL  1
    STATE VFRAC=0.0
    ANALYSIS ANAL-TYPE=TXY
    VARY PRES
    RANGE LIST=1.1
    VARY MOLEFRAC COMP=THF
    RANGE VARVALUE=RANGE LOWER=0.0 UPPER=1.0 NPOINT=50
    PARAM NPHASE=3

PROP-TABLE BINRY-4 FLASHCURVE
```

```
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    PROPERTIES UNIQUAC FREE-WATER=STEAM-TA SOLU-WATER=3  &
        TRUE-COMPS=YES
    MOLE-FLOW THF 1 /  ETHANOL  1
    STATE VFRAC=0.0
    ANALYSIS ANAL-TYPE=TXY
    VARY PRES
    RANGE LIST=1.013250000
    VARY MOLEFRAC COMP=THF
    RANGE VARVALUE=RANGE LOWER=0.0 UPPER=1.0 NPOINT=50
    PARAM NPHASE=3

PROP-TABLE PURE-1 PROPS
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    ANALYSIS ANAL-TYPE=PURE PURE-PROP='CP-M' UNITS='kJ/kg-K'  &
        PURE-PHASES= L
    MOLE-FLOW ETHANOL 1
    PROPERTIES UNIQUAC FREE-WATER=STEAM-TA SOLU-WATER=3  &
        TRUE-COMPS=YES
    VARY TEMP
    RANGE VARVALUE=RANGE LOWER=0 UPPER=100.0000000 NPOINT=50
    VARY PRES
    RANGE LIST=1.013250000
    PARAM

PROP-TABLE PURE-2 PROPS
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    ANALYSIS ANAL-TYPE=PURE PURE-PROP='MU' PURE-PHASES= L
    MOLE-FLOW ETHANOL 1
```

```
    PROPERTIES UNIQUAC FREE-WATER=STEAM-TA SOLU-WATER=3  &
        TRUE-COMPS=YES
    VARY TEMP
    RANGE VARVALUE=RANGE LOWER=0 UPPER=100.0000000 NPOINT=50
    VARY PRES
    RANGE LIST=1.013250000
    PARAM

PROP-TABLE MIX-1 FLASHCURVE
    IN-UNITS MET PRESSURE=bar TEMPERATURE=C DELTA-T=C PDROP=bar  &
        INVERSE-PRES='1/bar' SHORT-LENGTH=mm
    MOLE-FLOW ETHYLEGL 0.3 / WATER 0.7
    VARY PRES
    RANGE VARVALUE=LIST LIST=1.013250000
    VARY TEMP
    RANGE VARVALUE=RANGE LOWER=-20. UPPER=120. NPOINT=140
    PARAM
    TABULATE PROPERTIES=MASSCP RHO K VISCOSIT
;
;
;
;
;
```

ASPEN BLOCK REPORT

BOTTOMS DISTILLA ETOH FEED

STREAM ID	BOTTOMS	DISTILLA	ETOH	FEED
FROM :	B1	B1	----	----
TO :	----	----	B1	B1
SUBSTREAM: MIXED				
PHASE:	LIQUID	MIXED	LIQUID	LIQUID
COMPONENTS: KMOL/HR				
THF	5.5985	915.5985	0.0	921.2052
ETHANOL	1178.7581	3205.6580	51.5706	0.0
NITROGEN	0.0	2.9909-07	0.0	0.0
WATER	0.0	2.9909-07	0.0	0.0
ETHYLEGL	0.0	2.9909-07	0.0	0.0
TOTAL FLOW:				
KMOL/HR	1184.3567	4121.2565	51.5706	921.2052
KG/HR	5.4708+04	2.1370+05	2375.8072	6.6425+04
L/MIN	1246.2195	7002.1794	49.2342	1300.0000
STATE VARIABLES:				
TEMP C	80.2291	71.1919	20.0000	50.0000
PRES BAR	1.1000	1.0000	1.0000	1.0000
VFRAC	0.0	1.2173-03	0.0	0.0
LFRAC	1.0000	0.9988	1.0000	1.0000
SFRAC	0.0	0.0	0.0	0.0
ENTHALPY:				
CAL/MOL	-6.4448+04	-6.1376+04	-6.6426+04	-5.0851+04
CAL/GM	-1395.2220	-1183.6343	-1441.8778	-705.2169
CAL/SEC	-2.1203+07	-7.0263+07	-9.5156+05	-1.3012+07
ENTROPY:				

CAL/MOL-K	-77.5095	-82.1286	-83.2707	-103.7862
CAL/GM-K	-1.6780	-1.5839	-1.8075	-1.4393
DENSITY:				
MOL/CC	1.5839-02	9.8095-03	1.7458-02	1.1810-02
GM/CC	0.7317	0.5087	0.8043	0.8516
AVG MW	46.1921	51.8537	46.0690	72.1069

Table 25.6.1 Cash Flow Summary

Year	Percentage of Design Capacity	Product Unit Price	Sales	Capital Costs	Working Capital	Var Costs	Fixed Costs	Depreciation	Taxes	Net Earnings	Cash Flow	Cumulative Net Present Value at 15%
2020	0%		-	-	-	-	-	-	-	-	-	-
2021	0%		-	(7,232,600)	(12,354,000)	-	-	-	-	-	(19,586,600)	(17,031,800)
2022	45%	$30.00	256,368,200	-	(6,177,000)	(167,240,700)	(2,037,100)	(1,160,300)	(25,779,000)	60,151,100	55,134,400	24,657,700
2023	68%	$30.60	392,243,300	-	(6,177,000)	(255,878,200)	(2,077,800)	(986,300)	(39,990,300)	93,310,700	88,120,000	82,598,000
2024	90%	$31.21	533,450,900	-	-	(347,994,400)	(2,119,400)	(838,500)	(54,749,600)	127,749,000	128,587,600	156,118,400
2025	90%	$31.84	544,119,900	-	-	(354,954,200)	(2,161,800)	(714,800)	(55,886,700)	130,402,400	131,117,100	221,306,800
2026	90%	$32.47	555,002,300	-	-	(362,053,300)	(2,205,000)	(607,200)	(57,041,000)	133,095,700	133,702,900	279,110,200
2027	90%	$33.12	566,102,300	-	-	(369,294,400)	(2,249,100)	(516,000)	(58,212,900)	135,830,000	136,346,000	330,367,700
2028	90%	$33.78	577,424,400	-	-	(376,680,300)	(2,294,100)	(438,600)	(59,403,400)	138,608,000	139,046,600	375,822,300
2029	90%	$34.46	588,972,900	-	-	(384,213,900)	(2,340,000)	(372,800)	(60,613,900)	141,432,300	141,805,200	416,132,200
2030	90%	$35.15	600,752,300	-	-	(391,898,200)	(2,386,800)	(317,200)	(61,845,100)	144,305,200	144,622,300	451,880,600
2031	90%	$35.85	612,767,400	-	24,707,900	(399,736,100)	(2,434,500)	(269,200)	(63,098,300)	147,229,300	172,206,400	488,895,200